

Review

Ways to Address Perinatal Mast Cell Activation and Focal Brain Inflammation, including Response to SARS-CoV-2, in Autism Spectrum Disorder

Theoharis C. Theoharides ^{1,2,3,4} 

- ¹ Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology, Tufts University School of Medicine, 136 Harrison Avenue, Suite 304, Boston, MA 02111, USA; theoharis.theoharides@tufts.edu; Tel.: +1-(617)-636-6866; Fax: +1-(617)-636-2456
- ² School of Graduate Biomedical Sciences, Tufts University School of Medicine, Boston, MA 02111, USA
- ³ Department of Internal Medicine, Tufts University School of Medicine and Tufts Medical Center, Boston, MA 02111, USA
- ⁴ Department of Psychiatry, Tufts University School of Medicine and Tufts Medical Center, Boston, MA 02111, USA

Abstract: The prevalence of autism spectrum disorder (ASD) continues to increase, but no distinct pathogenesis or effective treatment are known yet. The presence of many comorbidities further complicates matters, making a personalized approach necessary. An increasing number of reports indicate that inflammation of the brain leads to neurodegenerative changes, especially during perinatal life, “short-circuiting the electrical system” in the amygdala that is essential for our ability to feel emotions, but also regulates fear. Inflammation of the brain can result from the stimulation of mast cells—found in all tissues including the brain—by neuropeptides, stress, toxins, and viruses such as SARS-CoV-2, leading to the activation of microglia. These resident brain defenders then release even more inflammatory molecules and stop “pruning” nerve connections, disrupting neuronal connectivity, lowering the fear threshold, and derailing the expression of emotions, as seen in ASD. Many epidemiological studies have reported a strong association between ASD and atopic dermatitis (eczema), asthma, and food allergies/intolerance, all of which involve activated mast cells. Mast cells can be triggered by allergens, neuropeptides, stress, and toxins, leading to disruption of the blood–brain barrier (BBB) and activation of microglia. Moreover, many epidemiological studies have reported a strong association between stress and atopic dermatitis (eczema) during gestation, which involves activated mast cells. Both mast cells and microglia can also be activated by SARS-CoV-2 in affected mothers during pregnancy. We showed increased expression of the proinflammatory cytokine IL-18 and its receptor, but decreased expression of the anti-inflammatory cytokine IL-38 and its receptor IL-36R, only in the amygdala of deceased children with ASD. We further showed that the natural flavonoid luteolin is a potent inhibitor of the activation of both mast cells and microglia, but also blocks SARS-CoV-2 binding to its receptor angiotensin-converting enzyme 2 (ACE2). A treatment approach should be tailored to each individual patient and should address hyperactivity/stress, allergies, or food intolerance, with the introduction of natural molecules or drugs to inhibit mast cells and microglia, such as liposomal luteolin.

Keywords: amygdala; autism spectrum disorder; brain; COVID-19; children; cytokines; flavonoids; inflammation; luteolin; mast cells; microglia; SARS-CoV-2; stress



Citation: Theoharides, T.C. Ways to Address Perinatal Mast Cell Activation and Focal Brain Inflammation, including Response to SARS-CoV-2, in Autism Spectrum Disorder. *J. Pers. Med.* **2021**, *11*, 860. <https://doi.org/10.3390/jpm11090860>

Academic Editors: Richard E. Frye, Richard Boles, Shannon Rose and Daniel Rossignol

Received: 27 June 2021

Accepted: 24 August 2021

Published: 29 August 2021

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2021 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

ASD is characterized by difficulties in communication and apparently purposeless repetitive movements [1–5]. The prevalence is estimated to be 1 in 54 children in the United States [6,7] and is associated with enormous economic burden [8–11]. However, ASD pathogenesis is still unknown. Moreover, most children with ASD have a number of comorbidities such as hyperactivity, gastrointestinal problems, allergies, and seizures [12–14],

making the development of effective treatments difficult and prompting the need for a personalized approach [15].

A number of risk factors during gestation [16], especially pre-eclampsia [17–19], preterm birth, and low birth weight [20–22], as well as atopic conditions, autoimmune diseases, [23–25] infection, and psychological stress, have been increasingly associated with higher risk of ASD in the offspring (Table 1) [26,27]. There have been many reports of different aspects of immune dysfunction in ASD [28–32]. In fact, maternal antibodies have been implicated in brain pathology in ASD [33], especially autoantibodies against proteins in the developing fetal brain [34–36]. We had proposed that focal inflammation in the amygdala may contribute to ASD [37–39] via activation of microglia [40–43]. The present manuscript is organized in different parts, stressing certain risk factors such as SARS-CoV2 infection, psychological stress, atopic conditions, and finally, treatment approaches.

Table 1. Conditions Associated with Higher Risk of ASD.

• Autoimmunity	[24,25,44]
• Allergies	[45–52]
• Asthma	[50,53]
• Atopic dermatitis	[54,55]
• COVID-19	[56,57]
• High fever	[58,59]
• Hypothyroidism	[24]
• Infection	[58,60,61]
• Inflammation	[38,39]
• Low birth weight/preterm birth	[16,20–22,62]
• Pre-eclampsia	[17–19]
• Mastocytosis	[63]
• Psoriasis	[23–25]
• Rheumatoid arthritis	[24]
• Stress	[16,62,64–72]

2. Infections and COVID-19

Infections [58,60,61] and high fever [58,59] during gestation have been associated with higher risk for ASD. However, there is very little information available on the effect of viruses, especially SARS-CoV-2, on the fetus. Viral proteins can interact with placenta cells [73]. One recent paper that reviewed findings from 101 women infected with SARS-CoV-2 reported that there is vertical transmission of SARS-CoV-2 from the mother to the infant, with adverse effects on the newborn [74]. However, two other papers reported negligible transmission [75,76]. However, transmission may not be required for the virus to induce neuroinflammation, as it may affect peripheral nerves [77] or the developing brain via the Spike protein directly affecting brain cells [78].

Recent publications reported increased perinatal complications in mothers infected with SARS-CoV-2 [56,79], especially pre-eclampsia [79] and premature birth [56,79], associated with inflammatory responses [80,81]. Pre-eclampsia is characterized by high levels of corticotropin-releasing hormone (CRH) [82,83], which is typically secreted from the hypothalamus under stress [84]. With respect to children infected with SARS-CoV-2, even though they have milder pulmonary symptoms than adults [85–91], a number of papers have reported the presence of Multisystem Inflammatory Syndrome in children (MIS-C) [92–94] and adolescents [95]. In such cases, symptoms typically occur 4–6 weeks after infection and are reminiscent of Kawasaki disease [96] but also include neurologic involvement [97]. Moreover, the clinical presentation is associated with elevated markers of inflammation and the presence of multiple autoantibodies [98], and one paper suggested that MIS may be a form of mast cell activation syndrome (MCAS) presenting with neuropsychiatric symptoms and brain fog [57]. In fact, perinatal brain inflammation [99] can contribute to the pathogenesis of neuropsychiatric disorders [100,101], including ASD [16,38,102]. A

recent NIH study reported blood vessel damage and perivascular inflammation in brains of deceased patients with COVID-19 [103].

COVID-19 has been associated with neurological [104–112], neurodegenerative [107,113], and mental [114–124] disorders, including ASD [125]. Moreover, it is now recognized that as many as 50% of those infected with SARS-CoV-2 [126] develop a post-acute syndrome known as “long-COVID syndrome” [127–129]. This syndrome is particularly associated with neurologic and psychiatric symptoms, especially brain fog, [128,130–132], as well as persistent fatigue apparently independent of the severity of the initial symptoms [133]. In fact, the Simons Fnd. (New York, NY, USA) recently announced the funding of longitudinal studies of mothers infected with maternal COVID-19 for increased risk for ASD. (<https://www.sfari.org/grant/maternal-covid-19-as-a-potential-risk-for-autism-supplemental-funding-for-ongoing-pregnancy-cohorts-request-for-applications/> (accessed on 1 June 2021).

The detrimental effects of stress, inflammation, and auto-immunity were discussed recently [134], especially with respect to COVID-19 [113] and mast cells [135]. A number of subsequent reviews have discussed neurobiological aspects [136] and neuroinflammation in the context of ASD [137–139]. In this paper, we discuss how environmental and stress stimuli trigger fetal or neonatal mast cells to secrete proinflammatory mediators, leading to focal inflammation in the amygdala, regulating emotions and fear (Figure 1) [140] and contributing to ASD [38,45,141]. We further propose a set of laboratory tests and approaches to better identify comorbidities and help each individual to be the best they can be.

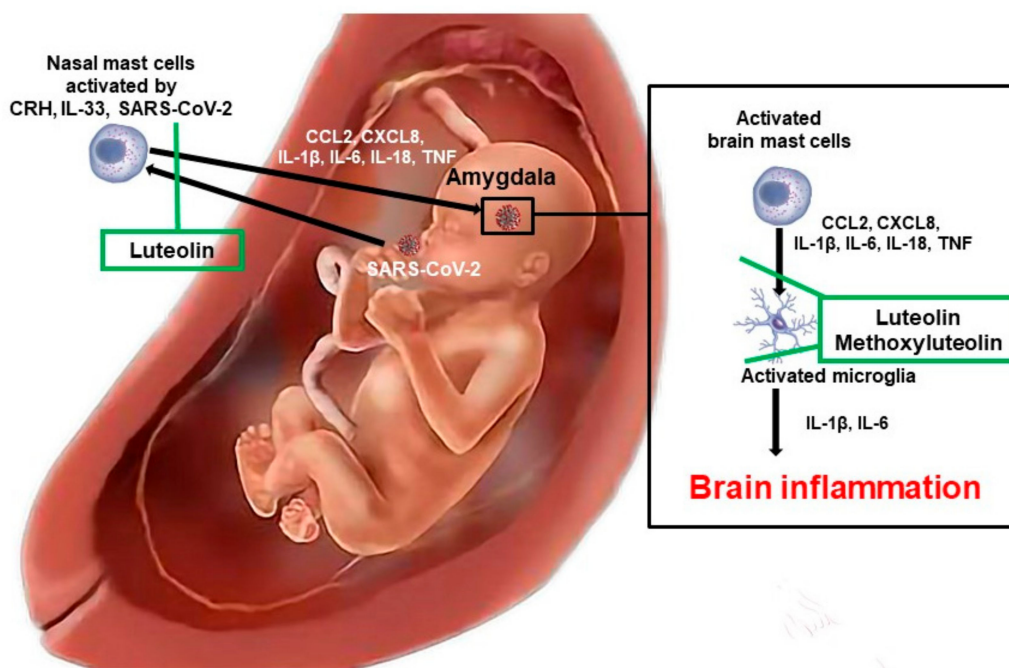


Figure 1. Diagrammatic representation of how SARS-CoV-2 could stimulate fetal mast cells and result in inflammation of the brain. SARS-CoV-2 could stimulate fetal or neonatal mast cells especially in the nose and enter the brain via the olfactory nerve tract, reaching the amygdala. There, it could further activate mast cells and microglia to release pro-inflammatory mediators, thus contributing to brain inflammation and ASD. Luteolin could block these processes.

3. Psychological Stress

Psychological stress can have pro-inflammatory effects [64,134] via CRH [142] stimulating mast cells [135]. One study showed that prenatal and early postnatal stress were associated with elevated serum levels of IL-6 in humans [143]. Another study reported that acute psychological stress increased the circulating levels of proinflammatory cytokines [144]. A longitudinal study of mothers' serum measurements during gestation

linked IL-6 to decreased executive function in their offspring [145]. We had shown that acute restraint stress significantly increased serum IL-6 in mice, which was entirely dependent on mast cells [146]. It is interesting that IL-6 has also been reported to promote human mast cell production and reactivity [147]. Moreover, prenatal stress or exposure to IL-6 resulted in increased microglia ramification in mice and was prevented by IL-6 blockade [148].

Psychological stress could also lead to increased vascular permeability [135]. This process also contributes to the disruption of the blood–brain barrier (BBB) [149,150] via release of CRH [151] and IL-6 [152], permitting entry into the brain of viral particles, cytokines, or other toxic substances, thus further exacerbating brain inflammation. Breakdown of the BBB has been reported in the developing brain following inflammation [153]. We further showed that restraint stress in rodents increased BBB permeability [149,150,154,155] via CRH stimulating mast cells [154,156,157]. The BBB typically prevents circulating toxic substances, but also immune cells, from entering the brain. The BBB is not fully developed until the third trimester [158–160] and is more vulnerable to toxins and drugs [161]. It was recently shown that common drugs such as acetaminophen (paracetamol) and cimetidine can enter the fetal brain in higher amounts than the adult brain [162]. Moreover, umbilical cord blood biomarkers indicative of acetaminophen exposure were significantly associated with the risk of ASD in childhood [163]. Hence, many atopic or pathogenic conditions, including exposure to certain drugs, could influence brain development during pregnancy or even lactation.

Stress associated with COVID-19 [134] can further affect the emotional state of individuals [118,119,164–167], especially social isolation, loneliness, and anxiety [168]. One study reported that prenatal stress was linked to higher risk of newborns developing attention-deficit hyperactivity disorder (ADHD) [65,66] and ASD [67–72]. A more recent study of 1638 pregnant women concluded that a high level of perceived stress through pregnancy, especially during the second trimester, was associated with an increased risk of the offspring developing ASD at 6 months of age [62]. Prenatal stress may lead to maternal immune dysregulation, thus contributing to ASD [70]. It is interesting that maternal psychological stress during pregnancy increased cord blood levels of IgE [169], suggesting that it could contribute to an increased risk in the fetus of developing allergic reactions or sensitivity to postnatal exposure to allergens. Psychological stress also increased the risk of childhood atopic dermatitis (AD) [170,171] and asthma [172–174]. To make matters worse, children with ASD cannot handle stress [175,176] and have an exacerbated sense of fear [39].

4. Mast Cell Activation

Infection with SARS-CoV-2 is primarily characterized by the release of a storm of pro-inflammatory cytokines [177–185], especially IL-6 [186–189] and IL-1 β [190,191]. Mast cells are a key source of such cytokines in COVID-19 [192–195] and could contribute to interstitial lung edema and immunothromboses [196].

We reported that children born to mothers with systemic mastocytosis [63], which is characterized by a greater number of hyperactive mast cells than in the general population [197], had a higher risk of developing ASD [1,2,7,198,199]. The word atopy is commonly used to denote a tendency, usually early in life, to become sensitized to and produce immune IgE to environmental antigens. Many epidemiological studies reported a strong association between atopic diseases and behavioral problems in general [200] and in ASD in particular [46,47]. Other epidemiological studies showed a strong association between risk for developing ASD and allergies [45,46,48–50], especially asthma [50,53] and atopic dermatitis (AD) [54], but also food hypersensitivity [12,201–205]. In fact, the presence of allergies was associated with elevated serum levels of autoantibodies against brain antigens in children with ASD [206]. Parental history of AD was strongly associated with children developing AD [207]. It was reported that maternal immune activation [208] and autoimmune diseases [209], especially psoriasis, but also allergies and asthma, were

associated with a higher risk of ASD [23]. In another study, almost 50% of children with ASD had relatives with rheumatoid diseases as compared to 26% in the control group [210]. In a recent large study, mothers who suffered from asthma, allergy, atopy, or eczema during pregnancy were associated with a higher risk of neuropsychiatric problems in children [55]. Three recent studies reported strong associations with ASD and food allergy [211] and food intolerance [202] that could lead to brain inflammation and cognitive impairment [212].

A recent publication showed that the mother's circulating immune IgE resulted in vertical transmission of AD in the newborn via stimulation of fetal mast cells [213]; both passive and active prenatal sensitization conferred allergen sensitivity [213]. This important paper indicated that fetal mast cells were functional and could be stimulated by specific IgE and allergens present in the mother during gestation. Even though these studies were limited to pulmonary and skin mast cells, reactivity could also extend to brain mast cells. In fact, prenatal allergen exposure was even shown to program lifelong changes in adult rats' social and sexual behavior, including effects on microglia activation and neonatal dendritic spine density [214]. Fetal mast cells could potentially respond to other stimuli such as neuropeptides and toxins, including the alarmin IL-33 [215,216], with detrimental effects on brain development, especially in premature babies [16].

Activated brain mast cells have been shown to contribute to cognitive dysfunction via microglia activation and neuronal apoptosis [217]. Mast cells are ubiquitous in the body [218] and are critical for allergic diseases [219], including mastocytosis [197]. However, mast cells also participate in inflammation [220,221] by secreting histamine and multiple pro-inflammatory cytokines and chemokines [222,223], including IL-1 β [224], IL-6 [225], and TNF [226]. Mast cells are also present in the brain, especially the meninges [227,228] and the median eminence [229], where they are located perivascularly, close to nerve endings positive for CRH [227]. We showed that stress stimulates mast cells via CRH [135] leading to increased dura vascular permeability, an effect that was absent in mast cell-deficient mice [230]. Moreover, mast cells can activate the hypothalamic–pituitary–adrenal (HPA) axis [142,231–233] via the release of histamine [234], IL-6 [152], and CRH [151]. Moreover, neurotensin [235] and substance P (SP) [236], neuropeptides implicated in inflammation, induced CRHR-1, thus creating an autocrine loop. Moreover, SP induced the ST2 receptor for IL-33 [226], further exacerbating mast cell activation by the combined action of neuropeptides and IL-33.

Mast cells respond not only to allergic but also to many other stimuli that can act alone or increase mast cell reactivity [197]. Mast cells can also be triggered by viruses [237] including SARS-CoV-2 [192,195]. In fact, gene expression of the coronavirus surface receptor angiotensin-converting enzyme 2 (ACE2) was recently shown to be induced by interferon [238], and mast cells can elicit strong pro-inflammatory and Type I interferon responses in the presence of viruses [239], implying an autocrine action on ACE2 expression. Following stimulation, mast cells release large amounts of pro-inflammatory mediators [222] such as histamine, tryptase, chemokines (e.g., CCL2, CCXL8) [240], and cytokines (IL-6, [225] IL-1 β [224], TNF [226]), especially when primed by IL-33 [216,241]. Histamine can stimulate macrophages to release IL-1 [242], which in turn stimulates mast cells to release IL-6 [225]. Mast cells can also secrete mitochondrial DNA (mtDNA) extracellularly [243], which serves as an alarmin and can stimulate pro-inflammatory mediator secretion from immune cells [244,245]. We reported elevated extracellular mtDNA in the serum of children with ASD [246]. In fact, it was recently reported that mtDNA may mediate prenatal environmental influences in ASD [247], was increased in the serum of COVID-19 patients, and correlated with disease severity [248]. Moreover, mast cells synthesize and release platelet-activating factor (PAF), which has been implicated in inflammation [249] and microthromboses [250] characterizing COVID-19. In fact, a recent paper reported a strong association across the globe with SARS-CoV-2 infection rates and levels of pollen known to be involved in upper respiratory system allergies, thus implicating mast cell activation [251]

5. Mast Cells and Microglia

Microglia are specialized resident macrophages of the Central Nervous System (CNS) with important functions in both health and disease. They are especially implicated in neuroinflammation [252–254] and neurodegenerative [252,255–257] diseases. Activation of microglia has been reported in ASD [41–43,258], as documented by the release of the pro-inflammatory mediators IL-1 β and CXCL8 [259]. Microglia were recently implicated in COVID-19 [260] and were also associated with neuroinflammation [261]. The transition of microglia from the resting to the activated proinflammatory phase is regulated by several intrinsic and extrinsic factors. Microglia can be activated by numerous molecules including pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated patterns (DAMPs) acting on Toll-like receptors (TLRs), but also in response to molecules released from mast cells, such as histamine and tryptase (Table 2) [39]. It was recently reported that elevated protein synthesis in microglia resulted in autism-like synaptic and behavioral changes in mice [262]. A dysfunctional neuroimmune cross-talk may result in a state of chronic fetal microglial activation leading to a disruption of neurogenesis and synaptic pruning [263], processes critical for the development of ASD.

Table 2. Molecules Activating Microglia.

-
- Chemokines (CCL2, CxCl8)
 - Cytokines (IL-1 β , IL-6, IL-18, TNF)
 - Histamine
 - Lipopolysaccharide (LPS)
 - Neuropeptides (CRH, HK-1, Neurotensin, SP)
 - Neurotransmitters
 - Pathogens (SARS-CoV-2)
 - Potassium
 - Prostaglandin D2
 - Proteases (MMP-3, Thrombin, Tryptase)
-

Mast cells interact with microglia in the brain [264], leading to their activation [264–267] and to neuroinflammation [266,268]. This effect is absent in mast cell-deficient mice [39,269]. Activation of mast cells [270,271] and microglia [272], especially in the hypothalamus [273], could lead to cognitive dysfunction [274]. Microglia express receptors for CRH [275] and could be further activated by stress, especially in association with COVID-19 [276]. Microglia also express receptors for neurotensin (NT) (Table 2) [277]. We reported that NT is increased in the serum of patients with ASD [278,279] and can activate human microglia to secrete pro-inflammatory molecules [259]. We also reported increased gene expression of the pro-inflammatory microRNA-155 (miR-155) in the amygdala of children with ASD [280], as well as reduced expression of the anti-inflammatory cytokine IL-38 [281]. Microglia also express TLRs [282] and were recently implicated in COVID-19 [260,283].

6. Treatment Approaches

It is critical to identify the presence of any atopy or allergies and food intolerance, especially the presence of Mast Cell Activation Syndrome (MCAS) [284,285] or systemic mastocytosis (SM) [197], by measuring the levels of the molecules listed in Table 3. Of note is IgG4 because it is involved in food intolerance and has been reported to be elevated in the plasma of children with ASD [286].

Table 3. Laboratory Tests for Diagnosis of Atopic Diseases.**Blood**

- IgA, IgG₁, IgG₄, IgE
- Immune IgE (RAST for alpha-gal, casein, dust, dust mites, egg, fungi, grass, gluten, pollen)
- Anti-IgE receptor antibody (basophil activation or histamine release test)
- CCL2, CXCL8 (IL-8)
- Chromogranin A *
- Eosinophilic cationic protein (ECP)
- Food Intolerance Panel
- Heparin
- IL-4, IL-6, IL-31, IL-33
- Prostaglandin D₂ (PGD₂)
- Tryptase

Urine collected for 24 h or first morning void (must be kept and sent cold)

- N-methylhistamine (NMH) or methylimidazole acetic acid (MIA)
- PGD₂
- 23BPG=2,3-Dinor-11 β -PGF_{2 α}

* Should be measured after one week of NO antacids, otherwise there is a high chance of false positive results. Elevated chromogranin A is not indicative of atopy, but of a somewhat similar condition called carcinoid syndrome associated with activated enterochromaffin cells in the gut.

It is also important to avoid histamine-rich foods, especially ripe tomatoes and avocados, cheeses, spinach, tangerines, spices, and sardines, which have been associated with histamine intolerance [287]. In this context, it is useful to conduct gene analysis for metabolizing enzymes, especially diamine oxidase (DAO), which breaks down histamine, and enzymes that break down phenols such as monoamine oxidase (MAO), catecholamine-ortho-methyl transferase (COMT), and phenol sulfur transferase (PST) to ascertain phenol intolerance that can contribute to hyperactivity. If DAO gene expression is defective and/or its activity in the blood is low, DAO supplements can be added about 30 min before meals, but one should be careful to avoid the common dyes and preservatives mentioned below.

Unfortunately, many medications, supplements, and vitamins contain “inactive” ingredients that are not tolerated by many children with ASD, leading to unexpected or worsening of behaviors. Such ingredients to be avoided include dyes, preservatives, gluten, monosodium glutamate (MSG), polyethylene glycol (PGE), galactosaccharide (GOS), salicylates, silicium, soy talc, and Twin 80. In addition, herbicides such as glyphosate and atrazine should be avoided, as they have been reported to stimulate mast cells and promote inflammation [288], besides their known neurotoxic effects.

One should choose the best tolerated antihistamine [289,290] from the list shown in Table 4, especially rupatadine, which also blocks mast cells, [291–293], and avoid large doses that may lead to confusion [294]. In fact, the Food and Drug Administration (FDA) recently warned that taking higher-than-recommended doses of diphenhydramine (Benadryl) can lead to serious heart problems, seizures, coma, or even death. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-problems-high-doses-allergy-medicine-diphenhydramine-benadryl> (accessed on 1 June 2021).

Table 4. Different histamine-1 receptor antagonists.

Generic Drug	(Trade Name)
Bilastine *	Nonsedating, non-metabolized
Cetirizine	Nonsedating
Cyproheptadine	Antiserotonergic
Diphenhydramine	Sedating
Hydroxyzine	Anxiolytic
Ketotifen *	Anti-eosinophilic
Loratadine	Nonsedating
Rupatadine *	Anti-PAF (Platelet activating factor), mast cell inhibitor
Tricyclic Antidepressants	
Amitriptyline	Weight gain
Doxepin	Also histamine-2 receptor antagonist
Phenothiazines	
Promethazine	Antiemetic
Prochlorperazine	Antiemetic, mast cell inhibitor

* Available only via compounding in the United States.

As discussed, anxiety, fear, and stress are major factors leading to hyperactivity. This should be investigated (by measuring total blood catecholamines and glutamate) and addressed with the use of a chamomile/passiflora/valerian extract or Ashwagandha [295,296]. If these are not sufficient, one should consider the beta-blocker propranolol that has good anti-anxiety properties without clouding the mental abilities and has also been reported to improve language in children with ASD [297]. Alternatively, one may recommend the use of alpha 2-receptor agonists [298] such as clonidine [299,300] and guanfacine [301,302], usually administered at bedtime especially since clonidine reduces sleep initiation latency and night awakening [303]. Moreover, caution should be exercised because such adrenergic blocking drugs may cause bradycardia and a drop in blood pressure. Cannabidiol (CBD) oil may be useful but it should be used with caution in individuals with atopic problems, because it has been reported to trigger the activation of cultured leukemic mast cells [304].

There has been considerable progress in defining drugs that block tyrosine kinases (TK) that are involved in mast cell proliferation [305]. The use of biologics for TNF [306,307] and IL-1 β , [308]; has significantly improved the treatment of inflammatory skin diseases. However, these agents have a number of limitations as they may cause paradoxical inflammation, reduced ability to fight infection, and cancer development [309]. In spite of such advances, there is no clinically effective inhibitor of human mast cell mediator secretion. Moreover, inhibitors of the tyrosine kinase c-kit receptor that reduce MC proliferation [310] do not inhibit mast cell activation [311]. There are still no clinically effective mast cell inhibitors [221,312]. Disodium cromoglycate (cromolyn), known as a “mast cell stabilizer,” had originally been shown to inhibit rat peritoneal MC histamine release [313]. However, cromolyn does not effectively inhibit either murine MC [314] or human MC [315–317] and has even been reported to potentiate histamine release from mast cells [318].

Instead of cromolyn, one should choose the best purity, source, and formulation of the flavonoids luteolin and quercetin [319–323]. These flavonoids are readily available and are generally considered safe [45,324–326]. Luteolin has broad anti-viral properties [327–329] and inhibits the entry of the corona virus into host cells [237,330,331]. Furthermore, luteolin better penetrates into the brain, inhibits both microglia [259,332–334] and mast cells [317,335], is neuroprotective [336–339], and has been reported to reduce neuroinflammation [337,340–342] and cognitive dysfunction [61,343–345], especially brain fog [346]. In fact, flavonoids were recently shown to improve cerebral cortical oxygenation and cognition in healthy adults. [347,348] Moreover, flavonoids induce the synthesis and secretion of neurotrophic factors, including brain-derived neurotrophic factor (BDNF) [77,349,350], known to be deficient in certain conditions associated with ASD, such as RETT syndrome [351]. The beneficial actions of luteolin are summarized in Table 5.

Table 5. Beneficial Actions of Luteolin *.

• Antagonizes SARS-CoV-2 Spike protein binding	[237,330,331,352]
• Has broad antiviral properties	[327–329]
• Improves cerebral cortical oxygenation and cognition	[347,348]
• Induces the synthesis and secretion of BDNF	[77,349–351]
• Inhibits serine proteases required for Spike protein processing	[353,354]
• Inhibits neuroinflammation	[340–342]
• Inhibits the release and action of PAF	[249,250]
• Inhibits mast cell stimulation by different triggers	[317,335]
• Inhibits microglia activation	[259,332–334]
• Interferes with coronavirus replication	[355]
• Is neuroprotective	[336–339]
• Reduces cognitive decline	[61,343–346]
• Reduces oxidative stress	[320]
• Regulates inflammasome activation	[356]

* Methoxyluteolin is more potent, metabolically stable, enters the brain more efficiently, and is better tolerated due to the absence of phenolic groups.

Luteolin and quercetin are not water-soluble and are difficult to absorb in powder form after oral administration [357], but their intestinal uptake can be greatly improved [358] in liposomal preparations using olive pomace oil [358]. In fact, such a luteolin formulation in olive pomace oil (NeuroProtek[®]) has been reported to improve ASD [359,360], while another one (BrainGain[®]) reduced brain fog [344]. The latter formulation also provided the additional neuroprotective [361–366] and anti-inflammatory [367,368] actions of olive pomace oil polyphenols, as well as the increase in memory induced by the olive oil component hydroxytyrosol [365,369].

The beneficial actions of these supplements could be combined with that of a unique, hypoallergenic skin lotion containing tetramethoxyflavone (GentleDerm[®]) [305], which can be applied on the forehead for direct absorption by temporal blood vessels. Tetramethoxyflavone (methoxyluteolin, methlut) is a more potent inhibitor of human mast cells than either quercetin or luteolin [317,335] and also inhibits human microglia [259,333].

The natural molecule berberine may be particularly useful in cases of PANS/PANDAS because of its antibacterial properties, but also because it can inhibit mast cells [370,371] and improve brain circulation [372]. In addition, high doses of Vitamin D3 are recommended, because this vitamin has been found to be present at low levels in mothers and/or children with ASD [371,373–375] and also decreases atopic responses [376]. When all fails, intravenous Ig may be administered [289].

7. Conclusions

It is critical to try to address each child individually (Table 6) [377] by first identifying any comorbidity, especially atopic diseases and hyperactivity, as well as any metabolic issue especially related to vitamins B1, B6, B12, folic acid/MTHFR, thyroid, or vitamin D3 deficiency, since these may be easily overcome. Inflammation of the brain may be reduced with the use of the natural flavonoid luteolin, especially when formulated in liposomal form in olive pomace oil that significantly increases oral absorption (BrainGain[®], PureLut[®], NeuroProtek[®] with FDA Certificate of Free Sale). The beneficial actions of these supplements could be augmented by the use of a unique, hypoallergenic skin lotion (GentleDerm[®]), which contains the more potent methoxyluteolin and can be applied on the temples for direct absorption by brain blood vessels. Thus, inhibiting the activation of mast cells and microglia not only would prevent vertical transmission of atopic disorders, but also may prevent inflammation of the brain and reduce the risk of the offspring developing neuropsychiatric disorders, especially ASD (US patents US 7,906,153; 8,268,365; 9050275).

Table 6. Treatment Approaches.

Hyperactivity
• Ashwagandha
• Chamomile/Passiflora/Valerian extract
• Clonidine or guanfacine
• C-Acetyl cysteine (NAC)
• Hydroxyzine
• Propranolol
Allergic Inflammation
• Berberine
• Luteolin *
• Rupatadine
• Vitamin D3
Neuronal fatigue
• Folate calcium or methylfolate
• Glutathione
• Methyl B12
• S-Adenosylmethionine (SAME)
OCD
• Aripiprazole
• Risperidone

* Children with phenol intolerance: PureLut[®]; NeuroProtek-Low Phenol[®], Adults with Brain Fog: BrainGain[®]; NeuroProtek[®], Adults also with allergies: FibroProtek[®], Adults also with interstitial cystitis: CystoProtek[®].

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Many thanks are due to Maria Theoharides for help drawing the figure.

Conflicts of Interest: The author declares no conflict of interest. The author is the recipient of US Patents 8,268,365, 9,050,275 and 9,176,146 covering brain inflammation and ASD. He is also the Scientific Director of Algonot, LLC (Florida, USA) that develops unique dietary supplements containing flavonoids.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
ADHD	Attention Deficit Hyperactivity Disorder
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
DAMPs	Damage-associated molecular patterns
HPA	Hypothalamic–pituitary–adrenal
MCAS	Mast Cell Activation Syndrome
MCI	Mild cognitive impairment
mtDNA	Mitochondrial DNA
MIS	Multisystem Inflammatory Syndrome
NT	Neurotensin
PANS	Pediatric Acute Neuropsychiatric Syndrome
PAMPs	Pathogen-associated molecular patterns
PAF	Platelet-activating factor
SP	Substance P
TLR	Toll-like receptor

References

1. Johnson, C.P.; Myers, S.M. Identification and evaluation of children with autism spectrum disorders. *Pediatrics* **2007**, *120*, 1183–1215. [[CrossRef](#)]
2. Lai, M.C.; Lombardo, M.V.; Baron-Cohen, S. Autism. *Lancet* **2014**, *383*, 896–910. [[CrossRef](#)]
3. Howes, O.D.; Rogdaki, M.; Findon, J.L.; Wichers, R.H.; Charman, T.; King, B.H.; Loth, E.; McAlonan, G.M.; McCracken, J.T.; Parr, J.; et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J. Psychopharmacol.* **2018**, *32*, 3–29. [[CrossRef](#)] [[PubMed](#)]
4. Braconnier, M.L.; Siper, P.M. Neuropsychological assessment in autism spectrum disorder. *Curr. Psychiatry Rep.* **2021**, *23*, 63. [[CrossRef](#)] [[PubMed](#)]
5. Iles, A. Autism spectrum disorders. *Prim. Care* **2021**, *48*, 461–473. [[CrossRef](#)]
6. Maenner, M.J.; Shaw, K.A.; Baio, J.; Washington, A.; Patrick, M.; DiRienzo, M.; Christensen, D.L.; Wiggins, L.D.; Pettygrove, S.; Andrews, J.G.; et al. Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveill. Summ.* **2020**, *69*, 1–12. [[CrossRef](#)]
7. Xu, G.; Strathearn, L.; Liu, B.; Bao, W. Prevalence of autism spectrum disorder among US children and adolescents, 2014–2016. *JAMA* **2018**, *319*, 81–82. [[CrossRef](#)]
8. Baxter, A.J.; Brugha, T.S.; Erskine, H.E.; Scheurer, R.W.; Vos, T.; Scott, J.G. The epidemiology and global burden of autism spectrum disorders. *Psychol. Med.* **2015**, *45*, 601–613. [[CrossRef](#)]
9. Leigh, J.P.; Du, J. Brief report: Forecasting the economic burden of autism in 2015 and 2025 in the United States. *J. Autism Dev. Disord.* **2015**, *12*, 4135–4139. [[CrossRef](#)] [[PubMed](#)]
10. Buescher, A.V.; Cidav, Z.; Knapp, M.; Mandell, D.S. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr.* **2014**, *168*, 721–728. [[CrossRef](#)] [[PubMed](#)]
11. Rogge, N.; Janssen, J. The economic costs of autism spectrum disorder: A literature review. *J. Autism Dev. Disord.* **2019**, *49*, 2873–2900. [[CrossRef](#)]
12. Xue, M.; Brimacombe, M.; Chaaban, J.; Zimmerman-Bier, B.; Wagner, G.C. Autism spectrum disorders: Concurrent clinical disorders. *J. Child Neurol.* **2008**, *23*, 6–13.
13. Bauman, M.L. Medical comorbidities in autism: Challenges to diagnosis and treatment. *Neurotherapeutics* **2010**, *7*, 320–327. [[CrossRef](#)]
14. Underwood, J.F.G.; Kendall, K.M.; Berrett, J.; Lewis, C.; Anney, R.; Van den Bree, M.B.; Hall, J. Autism spectrum disorder diagnosis in adults: Phenotype and genotype findings from a clinically derived cohort. *Br. J. Psychiatry* **2019**, *215*, 647–653. [[CrossRef](#)]
15. Mesleh, A.G.; Abdulla, S.A.; El-Agnaf, O. Paving the way toward personalized medicine: Current advances and challenges in Multi-OMICS approach in autism spectrum disorder for biomarkers discovery and patient stratification. *J. Pers. Med.* **2021**, *11*, 41. [[CrossRef](#)]
16. Angelidou, A.; Asadi, S.; Alysandratos, K.D.; Karagkouni, A.; Kourembanas, S.; Theoharides, T.C. Perinatal stress, brain inflammation and risk of autism—Review and proposal. *BMC Pediatr.* **2012**, *12*, 89. [[CrossRef](#)]
17. Wang, H.; Laszlo, K.D.; Gissler, M.; Li, F.; Zhang, J.; Yu, Y.; Li, J. Maternal hypertensive disorders and neurodevelopmental disorders in offspring: A population-based cohort in two Nordic countries. *Eur. J. Epidemiol.* **2021**, *36*, 519–530. [[CrossRef](#)]
18. Barron, A.; McCarthy, C.M.; O’Keeffe, G.W. Preeclampsia and neurodevelopmental outcomes: Potential pathogenic roles for inflammation and oxidative stress? *Mol. Neurobiol.* **2021**, *58*, 2734–2756. [[CrossRef](#)] [[PubMed](#)]
19. Katz, J.; Reichenberg, A.; Kolevzon, A. Prenatal and perinatal metabolic risk factors for autism: A review and integration of findings from population-based studies. *Curr. Opin. Psychiatry* **2021**, *34*, 94–104. [[CrossRef](#)] [[PubMed](#)]
20. Crump, C.; Sundquist, J.; Sundquist, K. Preterm or early term birth and risk of autism. *Pediatrics* **2021**, *148*, e2020032300. [[CrossRef](#)] [[PubMed](#)]
21. Stephens, B.E.; Bann, C.M.; Watson, V.E.; Sheinkopf, S.J.; Peralta-Carcelen, M.; Bodnar, A.; Yolton, K.; Goldstein, R.F.; Dusick, A.M.; Wilson-Costello, D.E.; et al. Screening for autism spectrum disorders in extremely preterm infants. *J. Dev. Behav. Pediatr.* **2012**, *33*, 535–541. [[CrossRef](#)]
22. McGowan, E.C.; Sheinkopf, S.J. Autism and preterm birth: Clarifying risk and exploring mechanisms. *Pediatrics* **2021**, *148*, e2021051978. [[CrossRef](#)]
23. Croen, L.A.; Grether, J.K.; Yoshida, C.K.; Odouli, R.; Van de Water, J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: A case-control study. *Arch. Pediatr. Adolesc. Med.* **2005**, *159*, 151–157. [[CrossRef](#)] [[PubMed](#)]
24. Wu, S.; Ding, Y.; Wu, F.; Li, R.; Xie, G.; Hou, J.; Mao, P. Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **2015**, *55*, 322–332. [[CrossRef](#)]
25. Lee, H.; Hsu, J.W.; Tsai, S.J.; Huang, K.L.; Bai, Y.M.; Su, T.P.; Chen, T.J.; Chen, M.H. Risk of attention deficit hyperactivity and autism spectrum disorders among the children of parents with autoimmune diseases: A nationwide birth cohort study. *Eur. Child Adolesc. Psychiatry* **2021**, 1–9. [[CrossRef](#)]
26. Matelski, L.; van de Water, J. Risk factors in autism: Thinking outside the brain. *J. Autoimmun.* **2016**, *67*, 1–7. [[CrossRef](#)]
27. Muhle, R.A.; Reed, H.E.; Stratigos, K.A.; Veenstra-Vanderweele, J. The emerging clinical neuroscience of autism spectrum disorder: A review. *JAMA Psychiatry* **2018**, *75*, 514–523. [[CrossRef](#)]

28. Zimmerman, A.W.; Jyonouchi, H.; Comi, A.M.; Connors, S.L.; Milstien, S.; Varsou, A.; Heyes, M.P. Cerebrospinal fluid and serum markers of inflammation in autism. *Pediatr. Neurol.* **2005**, *33*, 195–201. [[CrossRef](#)]
29. Estes, M.L.; McAllister, A.K. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. *Nat. Rev. Neurosci.* **2015**, *16*, 469–486. [[CrossRef](#)] [[PubMed](#)]
30. Meltzer, A.; van de Water, J. The role of the immune system in autism spectrum disorder. *Neuropsychopharmacology* **2017**, *42*, 284–298. [[CrossRef](#)] [[PubMed](#)]
31. Matta, S.M.; Hill-Yardin, E.L.; Crack, P.J. The influence of neuroinflammation in autism spectrum disorder. *Brain Behav. Immun.* **2019**, *79*, 75–90. [[CrossRef](#)]
32. Hughes, H.K.; Mills, K.E.; Rose, D.; Ashwood, P. Immune dysfunction and autoimmunity as pathological mechanisms in autism spectrum disorders. *Front. Cell Neurosci.* **2018**, *12*, 405. [[CrossRef](#)]
33. Kowal, C.; Athanassiou, A.; Chen, H.; Diamond, B. Maternal antibodies and developing blood-brain barrier. *Immunol. Res.* **2015**, *63*, 18–25. [[CrossRef](#)]
34. Edmiston, E.; Ashwood, P.; van de Water, J. Autoimmunity, autoantibodies, and autism spectrum disorder. *Biol. Psychiatry* **2017**, *81*, 383–390. [[CrossRef](#)] [[PubMed](#)]
35. Jones, K.L.; van de Water, J. Maternal autoantibody related autism: Mechanisms and pathways. *Mol. Psychiatry* **2019**, *24*, 252–265. [[CrossRef](#)] [[PubMed](#)]
36. Mazon-Cabrera, R.; Vandormael, P.; Somers, V. Antigenic targets of patient and maternal autoantibodies in autism spectrum disorder. *Front. Immunol.* **2019**, *10*, 1474. [[CrossRef](#)] [[PubMed](#)]
37. Theoharides, T.C.; Zhang, B. Neuro-inflammation, blood-brain barrier, seizures and autism. *J. Neuroinflamm.* **2011**, *8*, 168. [[CrossRef](#)] [[PubMed](#)]
38. Theoharides, T.C.; Asadi, S.; Patel, A.B. Focal brain inflammation and autism. *J. Neuroinflamm.* **2013**, *10*, 46. [[CrossRef](#)] [[PubMed](#)]
39. Theoharides, T.C.; Kavalioti, M.; Tsilioni, I. Mast cells, stress, fear and autism spectrum disorder. *Int. J. Mol. Sci.* **2019**, *20*, 3611. [[CrossRef](#)] [[PubMed](#)]
40. Rodriguez, J.I.; Kern, J.K. Evidence of microglial activation in autism and its possible role in brain underconnectivity. *Neuron Glia Biol.* **2011**, *7*, 205–213. [[CrossRef](#)] [[PubMed](#)]
41. Gupta, S.; Ellis, S.E.; Ashar, F.N.; Moes, A.; Bader, J.S.; Zhan, J.; West, A.B.; Arking, D.E. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nat. Commun.* **2014**, *5*, 5748. [[CrossRef](#)]
42. Koyama, R.; Ikegaya, Y. Microglia in the pathogenesis of autism spectrum disorders. *Neurosci. Res.* **2015**, *100*, 1–5. [[CrossRef](#)]
43. Takano, T. Role of microglia in autism: Recent advances. *Dev. Neurosci.* **2015**, *37*, 195–202. [[CrossRef](#)]
44. Theoharides, T.C.; Asadi, S.; Panagiotidou, S.; Weng, Z. The “missing link” in autoimmunity and autism: Extracellular mitochondrial components secreted from activated live mast cells. *Autoimmun. Rev.* **2013**, *12*, 1136–1142. [[CrossRef](#)] [[PubMed](#)]
45. Theoharides, T.C.; Tsilioni, I.; Patel, A.B.; Doyle, R. Atopic diseases and inflammation of the brain in the pathogenesis of autism spectrum disorders. *Transl. Psychiatry* **2016**, *6*, e844. [[CrossRef](#)]
46. Liao, T.C.; Lien, Y.T.; Wang, S.; Huang, S.L.; Chen, C.Y. Comorbidity of atopic disorders with autism spectrum disorder and attention deficit/hyperactivity disorder. *J. Pediatr.* **2016**, *171*, 248–255. [[CrossRef](#)] [[PubMed](#)]
47. Theoharides, T.C. Is a subtype of autism an “allergy of the brain”? *Clin. Ther.* **2013**, *35*, 584–591. [[CrossRef](#)]
48. Magalhaes, E.S.; Pinto-Mariz, F.; Bastos-Pinto, S.; Pontes, A.T.; Prado, E.A.; Deazevedo, L.C. Immune allergic response in Asperger syndrome. *J. Neuroimmunol.* **2009**, *216*, 108–112. [[CrossRef](#)] [[PubMed](#)]
49. Jyonouchi, H. Autism spectrum disorders and allergy: Observation from a pediatric allergy/immunology clinic. *Expert. Rev. Clin. Immunol.* **2010**, *6*, 397–411. [[CrossRef](#)] [[PubMed](#)]
50. Lyall, K.; van de Water, J.; Ashwood, P.; Hertz-Picciotto, I. Asthma and allergies in children with autism spectrum disorders: Results from the charge study. *Autism Res.* **2015**, *8*, 567–574. [[CrossRef](#)] [[PubMed](#)]
51. Angelidou, A.; Alysandratos, K.D.; Asadi, S.; Zhang, B.; Francis, K.; Vasiadi, M.; Kalogeromitros, D.; Theoharides, T.C. Brief Report: “Allergic Symptoms” in children with Autism Spectrum Disorders. More than meets the eye? *J. Autism Dev. Disord.* **2011**, *41*, 1579–1585. [[CrossRef](#)] [[PubMed](#)]
52. Saitoh, B.Y.; Tanaka, E.; Yamamoto, N.; Kruining, D.V.; Iinuma, K.; Nakamuta, Y.; Yamaguchi, H.; Yamasaki, R.; Matsumoto, K.; Kira, J.I. Early postnatal allergic airway inflammation induces dystrophic microglia leading to excitatory postsynaptic surplus and autism-like behavior. *Brain Behav. Immun.* **2021**, *95*, 362–380. [[CrossRef](#)] [[PubMed](#)]
53. Kotey, S.; Ertel, K.; Whitcomb, B. Co-occurrence of autism and asthma in a nationally-representative sample of children in the United States. *J. Autism Dev. Disord.* **2014**, *44*, 3083–3088. [[CrossRef](#)] [[PubMed](#)]
54. Billeci, L.; Tonacci, A.; Tartarisco, G.; Ruta, L.; Pioggia, G.; Gangemi, S. Association between atopic dermatitis and autism spectrum disorders: A systematic review. *Am. J. Clin. Dermatol.* **2015**, *16*, 371–388. [[CrossRef](#)]
55. Patel, S.; Cooper, M.N.; Jones, H.; Whitehouse, A.J.O.; Dale, R.C.; Guastella, A.J. Maternal immune-related conditions during pregnancy may be a risk factor for neuropsychiatric problems in offspring throughout childhood and adolescence. *Psychol. Med.* **2020**, 1–11. [[CrossRef](#)]
56. Angelidou, A.; Sullivan, K.; Melvin, P.R.; Shui, J.E.; Goldfarb, I.T.; Bartolome, R.; Chaudhary, N.; Vaidya, R.; Culic, I.; Singh, R.; et al. Association of maternal perinatal SARS-CoV-2 infection with neonatal outcomes during the COVID-19 pandemic in Massachusetts. *JAMA Netw. Open* **2021**, *4*, e217523. [[CrossRef](#)]

57. Theoharides, T.C.; Conti, P. COVID-19 and multisystem inflammatory syndrome, or is it mast cell activation syndrome? *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 1633–1636.
58. Holingue, C.; Brucato, M.; Ladd-Acosta, C.; Hong, X.; Volk, H.; Mueller, N.T.; Wang, X.; Fallin, M.D. Interaction between maternal immune activation and antibiotic use during pregnancy and child risk of autism spectrum disorder. *Autism Res.* **2020**, *13*, 2230–2241. [[CrossRef](#)]
59. Wilkerson, D.S.; Volpe, A.G.; Dean, R.S.; Titus, J.B. Perinatal complications as predictors of infantile autism. *Int. J. Neurosci.* **2002**, *112*, 1085–1098. [[CrossRef](#)]
60. Tioleco, N.; Silberman, A.E.; Stratigos, K.; Banerjee-Basu, S.; Spann, M.N.; Whitaker, A.H.; Turner, J.B. Prenatal maternal infection and risk for autism in offspring: A meta-analysis. *Autism Res.* **2021**, *14*, 1296–1316. [[CrossRef](#)]
61. Yao, Z.H.; Yao, X.L.; Zhang, Y.; Zhang, S.F.; Hu, J.C. Luteolin could improve cognitive dysfunction by inhibiting neuroinflammation. *Neurochem. Res.* **2018**, *43*, 806–820. [[CrossRef](#)]
62. Shen, Q.; Zhang, Q.; Zhao, J.; Huang, Z.; Wang, X.; Ni, M.; Tang, Z.; Liu, Z. Association between maternal perceived stress in all trimesters of pregnancy and infant atopic dermatitis: A prospective birth cohort study. *Front. Pediatr.* **2020**, *8*, 526994. [[CrossRef](#)] [[PubMed](#)]
63. Theoharides, T.C. Autism spectrum disorders and mastocytosis. *Int. J. Immunopathol. Pharmacol.* **2009**, *22*, 859–865. [[CrossRef](#)]
64. Theoharides, T.C. Effect of stress on neuroimmune processes. *Clin. Ther.* **2020**, *42*, 1007–1014. [[CrossRef](#)]
65. Ronald, A.; Pennell, C.E.; Whitehouse, A.J. Prenatal maternal stress associated with ADHD and autistic traits in early childhood. *Front. Psychol.* **2010**, *1*, 223. [[CrossRef](#)]
66. Okano, L.; Ji, Y.; Riley, A.W.; Wang, X. Maternal psychosocial stress and children’s ADHD diagnosis: A prospective birth cohort study. *J. Psychosom. Obstet. Gynaecol.* **2019**, *40*, 217–225. [[CrossRef](#)] [[PubMed](#)]
67. MacKinnon, N.; Kingsbury, M.; Mahedy, L.; Evans, J.; Colman, I. The association between prenatal stress and externalizing symptoms in childhood: Evidence from the avon longitudinal study of parents and children. *Biol. Psychiatry* **2018**, *83*, 100–108. [[CrossRef](#)] [[PubMed](#)]
68. Beversdorf, D.Q.; Manning, S.E.; Hillier, A.; Anderson, S.L.; Nordgren, R.E.; Walters, S.E.; Nagaraja, H.N.; Cooley, W.C.; Gaelic, S.E.; Bauman, M.L. Timing of prenatal stressors and autism. *J. Autism. Dev. Disord.* **2005**, *35*, 471–478. [[CrossRef](#)]
69. Crafa, D.; Warfa, N. Maternal migration and autism risk: Systematic analysis. *Int. Rev. Psychiatry* **2015**, *27*, 64–71. [[CrossRef](#)] [[PubMed](#)]
70. Beversdorf, D.Q.; Stevens, H.E.; Margolis, K.G.; van de Water, J. Prenatal stress and maternal immune dysregulation in autism spectrum disorders: Potential points for intervention. *Curr. Pharm. Des.* **2019**, *25*, 4331–4343. [[CrossRef](#)]
71. Evans, D.W.; Canavera, K.; Kleinpeter, F.L.; Maccubbin, E.; Taga, K. The fears, phobias and anxieties of children with autism spectrum disorders and Down syndrome: Comparisons with developmentally and chronologically age matched children. *Child Psychiatry Hum. Dev.* **2005**, *36*, 3–26. [[CrossRef](#)] [[PubMed](#)]
72. Beversdorf, D.Q.; Stevens, H.E.; Jones, K.L. Prenatal stress, maternal immune dysregulation, and their association with autism spectrum disorders. *Curr. Psychiatry Rep.* **2018**, *20*, 76. [[CrossRef](#)] [[PubMed](#)]
73. Fuentes-Zacarias, P.; Murrieta-Coxca, J.M.; Gutierrez-Samudio, R.N.; Schmidt, A.; Markert, U.R.; Morales-Prieto, D.M. Pregnancy and pandemics: Interaction of viral surface proteins and placenta cells. *Biochim. Biophys. Acta Mol. Basis. Dis.* **2021**, *1867*, 166218. [[CrossRef](#)] [[PubMed](#)]
74. Facchetti, F.; Bugatti, M.; Drera, E.; Tripodo, C.; Sartori, E.; Cancila, V.; Papaccio, M.; Castellani, R.; Casola, S.; Boniotti, M.B.; et al. SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of Placenta. *EBioMedicine* **2020**, *59*, 102951. [[CrossRef](#)] [[PubMed](#)]
75. Sharma, R.; Seth, S.; Sharma, R.; Yadav, S.; Mishra, P.; Mukhopadhyay, S. Perinatal outcome and possible vertical transmission of coronavirus disease 2019: Experience from North India. *Clin. Exp. Pediatr.* **2021**, *64*, 239–246. [[CrossRef](#)] [[PubMed](#)]
76. Kaklamanos, E.G.; Menexes, G.; Makrygiannakis, M.A.; Topitsoglou, V.; Kalfas, S. Tooth wear in a sample of community-dwelling elderly Greeks. *Oral Health Prev. Dent.* **2020**, *18*, 133–138.
77. Moosavi, F.; Hosseini, R.; Saso, L.; Firuzi, O. Modulation of neurotrophic signaling pathways by polyphenols. *Drug Des. Devel. Ther.* **2016**, *10*, 23–42.
78. Theoharides, T.C.; Conti, P. Be aware of SARS-CoV-2 spike protein: There is more than meets the eye. *J. Biol. Regul. Homeost. Agents* **2021**, *35*, 833–838.
79. Villar, J.; Ariff, S.; Gunier, R.B.; Thiruvengadam, R.; Rauch, S.; Kholin, A.; Roggero, P.; Prefumo, F.; do Vale, M.S.; Cardona-Perez, J.A. Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: The INTERCOVID multinational cohort study. *JAMA Pediatr.* **2021**, *175*, 817–826. [[CrossRef](#)]
80. Lu-Culligan, A.; Chavan, A.R.; Vijayakumar, P.; Irshaid, L.; Courchaine, E.M.; Milano, K.M.; Tang, Z.; Pope, S.D.; Song, E.; Vogels, C.F. SARS-CoV-2 infection in pregnancy is associated with robust inflammatory response at the maternal-fetal interface. *medRxiv* **2021**. [[CrossRef](#)]
81. Narang, K.; Enninga, E.A.L.; Gunaratne, M.D.S.K.; Ibiroga, E.R.; Trad, A.T.A.; Elrefaei, A.; Theiler, R.N.; Ruano, R.; Szymanski, L.M.; Chakraborty, R. SARS-CoV-2 infection and COVID-19 during pregnancy: A multidisciplinary review. *Mayo Clin. Proc.* **2020**, *95*, 1750–1765. [[CrossRef](#)]
82. Grammatopoulos, D.K.; Hillhouse, E.W. Role of corticotropin-releasing hormone in onset of labour. *Lancet* **1999**, *354*, 1546–1549. [[CrossRef](#)]

83. Ng, E.K.; Leung, T.N.; Tsui, N.B.; Lau, T.K.; Panesar, N.S.; Chiu, R.W.; Lo, Y.M. The concentration of circulating corticotropin-releasing hormone mRNA in maternal plasma is increased in preeclampsia. *Clin. Chem.* **2003**, *49*, 727–731. [[CrossRef](#)]
84. Chrousos, G.P. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N. Engl. J. Med.* **1995**, *332*, 1351–1362. [[CrossRef](#)] [[PubMed](#)]
85. She, J.; Liu, L.; Liu, W. COVID-19 epidemic: Disease characteristics in children. *J. Med. Virol.* **2020**, *92*, 747–754. [[CrossRef](#)] [[PubMed](#)]
86. Dong, Y.; Mo, X.; Hu, Y.; Qi, X.; Jiang, F.; Jiang, Z.; Tong, S. Epidemiology of COVID-19 among Children in China. *Pediatrics* **2020**, *145*, e20200702. [[CrossRef](#)] [[PubMed](#)]
87. Ludvigsson, J.F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* **2020**, *109*, 1088–1095. [[CrossRef](#)]
88. Tian, S.; Hu, N.; Lou, J.; Chen, K.; Kang, X.; Xiang, Z.; Chen, H.; Wang, D.; Liu, N.; Liu, D. Characteristics of COVID-19 infection in Beijing. *J. Infect.* **2020**, *80*, 401–406. [[CrossRef](#)]
89. Ciotti, M.; Angeletti, S.; Minieri, M.; Giovannetti, M.; Benvenuto, D.; Pascarella, S.; Sagnelli, C.; Bianchi, M.; Bernardini, S.; Ciccozzi, M. COVID-19 outbreak: An overview. *Chemotherapy* **2019**, *64*, 215–223. [[CrossRef](#)] [[PubMed](#)]
90. Hong, H.; Wang, Y.; Chung, H.T.; Chen, C.J. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatr. Neonatol.* **2020**, *61*, 131–132. [[CrossRef](#)]
91. Castagnoli, R.; Votto, M.; Licari, A.; Brambilla, I.; Bruno, R.; Perlini, S.; Rovida, F.; Baldanti, F.; Marseglia, G.L. Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review. *JAMA Pediatr.* **2020**, *174*, 882–889. [[CrossRef](#)] [[PubMed](#)]
92. Greene, A.G.; Saleh, M.; Roseman, E.; Sinert, R. Toxic shock-like syndrome and COVID-19: A case report of multisystem inflammatory syndrome in children (MIS-C). *Am. J. Emerg. Med.* **2020**, *38*, 30492–30497. [[CrossRef](#)] [[PubMed](#)]
93. Levin, M. Childhood multisystem inflammatory syndrome—A new challenge in the pandemic. *N. Engl. J. Med.* **2020**, *383*, 393–395. [[CrossRef](#)]
94. Feldstein, L.R.; Rose, E.B.; Horwitz, S.M.; Collins, J.P.; Newhams, M.M.; Son, M.B.F.; Newburger, J.W.; Kleinman, L.C.; Heidemann, S.M.; Martin, A.A. Multisystem inflammatory syndrome in U.S. children and adolescents. *N. Engl. J. Med.* **2020**, *383*, 334–346. [[CrossRef](#)] [[PubMed](#)]
95. Jiang, L.; Tang, K.; Levin, M.; Irfan, O.; Morris, S.K.; Wilson, K.; Klein, J.D.; Bhutta, Z.A. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect. Dis.* **2020**, *20*, e276–e288. [[CrossRef](#)]
96. Rowley, A.H. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. *Nat. Rev. Immunol.* **2020**, *20*, 453–454. [[CrossRef](#)] [[PubMed](#)]
97. Schwartz, L.B.; Bradford, T.R.; Littman, B.H.; Wintroub, B.U. The fibrinolytic activity of purified tryptase from human lung mast cells. *J. Immunol.* **1985**, *135*, 2762–2767.
98. Consiglio, C.R.; Cotugno, N.; Sardh, F.; Pou, C.; Amodio, D.; Rodriguez, L.; Tan, Z.; Zicari, S.; Ruggiero, A.; Pascucci, G.R. The immunology of multisystem inflammatory syndrome in children with COVID-19. *Cell* **2020**, *183*, 968–981. [[CrossRef](#)]
99. Hagberg, H.; Gressens, P.; Mallard, C. Inflammation during fetal and neonatal life: Implications for neurologic and neuropsychiatric disease in children and adults. *Ann. Neurol.* **2012**, *71*, 444–457. [[CrossRef](#)] [[PubMed](#)]
100. Jones, K.A.; Thomsen, C. The role of the innate immune system in psychiatric disorders. *Mol. Cell Neurosci.* **2013**, *53*, 52–62. [[CrossRef](#)]
101. Chavarria, A.; Alcocer-Varela, J. Is damage in central nervous system due to inflammation? *Autoimmun. Rev.* **2004**, *3*, 251–260. [[CrossRef](#)] [[PubMed](#)]
102. Le Belle, J.E.; Sperry, J.; Ngo, A.; Ghochani, Y.; Laks, D.R.; Lopez-Aranda, M.; Silva, A.J.; Kornblum, H.I. Maternal inflammation contributes to brain overgrowth and autism-associated behaviors through altered redox signaling in stem and progenitor cells. *Stem Cell Rep.* **2014**, *3*, 725–734. [[CrossRef](#)] [[PubMed](#)]
103. Lee, M.H.; Perl, D.P.; Nair, G.; Li, W.; Maric, D.; Murray, H.; Dodd, S.J.; Koretsky, A.P.; Watts, J.A.; Cheung, V.; et al. Microvascular injury in the brains of patients with Covid-19. *N. Engl. J. Med.* **2020**, *384*, 481–483. [[CrossRef](#)]
104. Helms, J.; Kremer, S.; Merdji, H.; Clere-Jehl, R.; Schenck, M.; Kummerlen, C.; Collange, O.; Boulay, C.; Fafi-Kremer, S.; Ohana, M. Neurologic features in severe SARS-CoV-2 infection. *N. Engl. J. Med.* **2020**, *382*, 2268–2270. [[CrossRef](#)] [[PubMed](#)]
105. Fotuhi, M.; Mian, A.; Meysami, S.; Raji, C.A. Neurobiology of COVID-19. *J. Alzheimers Dis.* **2020**, *76*, 3–19. [[CrossRef](#)]
106. Najjar, S.; Najjar, A.; Chong, D.J.; Pramanik, B.K.; Kirsch, C.; Kuzniecky, R.I.; Pacia, S.V.; Azhar, S. Central nervous system complications associated with SARS-CoV-2 infection: Integrative concepts of pathophysiology and case reports. *J. Neuroinflamm.* **2020**, *17*, 231. [[CrossRef](#)]
107. Singh, A.K.; Bhushan, B.; Maurya, A.; Mishra, G.; Singh, S.K.; Awasthi, R. Novel coronavirus disease 2019 (COVID-19) and neurodegenerative disorders. *Dermatol. Ther.* **2020**, *33*, e13591. [[CrossRef](#)]
108. Liotta, E.M.; Batra, A.; Clark, J.R.; Shlobin, N.A.; Hoffman, S.C.; Orban, Z.S.; Korálnik, I.J. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann. Clin. Transl. Neurol.* **2020**, *7*, 2221–2230. [[CrossRef](#)]
109. Korálnik, I.J.; Tyler, K.L. COVID-19: A global threat to the nervous system. *Ann. Neurol.* **2020**, *88*, 1–11. [[CrossRef](#)]
110. Nepal, G.; Rehrig, J.H.; Shrestha, G.S.; Shing, Y.K.; Yadav, J.K.; Ojha, R.; Pokhrel, G.; Tu, Z.L.; Huang, D.Y. Neurological manifestations of COVID-19: A systematic review. *Crit. Care* **2020**, *24*, 421. [[CrossRef](#)] [[PubMed](#)]

111. Favas, T.T.; Dev, P.; Chaurasia, R.N.; Chakravarty, K.; Mishra, R.; Joshi, D.; Mishra, V.N.; Kumar, A.; Singh, V.K.; Pandey, M.; et al. Neurological manifestations of COVID-19: A systematic review and meta-analysis of proportions. *Neurol. Sci.* **2020**, *41*, 3437–3470. [[CrossRef](#)] [[PubMed](#)]
112. Nazari, S.; Azari, J.A.; Mirmoenei, S.; Sadeghian, S.; Heidari, M.E.; Assarzagdegan, F.; Puormand, S.M.; Ebadi, H.; Fathi, D. Central nervous system manifestations in COVID-19 patients: A systematic review and meta-analysis. *Brain Behav.* **2021**, *11*, e02025. [[CrossRef](#)]
113. Kempuraj, D.; Selvakumar, G.P.; Ahmed, M.E.; Raikwar, S.P.; Thangavel, R.; Khan, A.; Zaheer, S.A.; Iyer, S.S.; Burton, C.; James, D.; et al. COVID-19, mast cells, cytokine storm, psychological stress, and neuroinflammation. *Neuroscientist* **2020**, *26*, 402–414. [[CrossRef](#)]
114. Schirinzi, T.; Landi, D.; Liguori, C. COVID-19: Dealing with a potential risk factor for chronic neurological disorders. *J. Neurol.* **2020**, *268*, 1171–1178. [[CrossRef](#)] [[PubMed](#)]
115. Ongur, D.; Perlis, R.; Goff, D. Psychiatry and COVID-19. *JAMA* **2020**, *324*, 1149–1150. [[CrossRef](#)]
116. Vindegaard, N.; Benros, M.E. COVID-19 pandemic and mental health consequences: Systematic review of the current evidence. *Brain Behav. Immun.* **2020**, *89*, 531–542. [[CrossRef](#)]
117. Pfefferbaum, B.; North, C.S. Mental health and the Covid-19 pandemic. *N. Engl. J. Med.* **2020**, *383*, 510–512. [[CrossRef](#)]
118. Xiang, Y.-T.; Yang, Y.; Li, W.; Zhang, L.; Zhang, Q.; Cheung, T.; Ng, C. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *Lancet Psychiatry* **2020**, *7*, 228–229. [[CrossRef](#)]
119. Gordon, J.A.; Borja, S.E. The COVID-19 pandemic: Setting the mental health research agenda. *Biol. Psychiatry* **2020**, *88*, 130–131. [[CrossRef](#)] [[PubMed](#)]
120. Taquet, M.; Luciano, S.; Geddes, J.R.; Harrison, P.J. Bidirectional associations between COVID-19 and psychiatric disorder: Retrospective cohort studies of 62,354 COVID-19 cases in the USA. *Lancet Psychiatry* **2021**, *8*, 130–140. [[CrossRef](#)]
121. Steardo, L., Jr.; Steardo, L.; Verkhatsky, A. Psychiatric face of COVID-19. *Transl. Psychiatry* **2020**, *10*, 261. [[CrossRef](#)]
122. Shader, R.I. COVID-19 and depression. *Clin. Ther.* **2020**, *42*, 962–963. [[CrossRef](#)]
123. Smith, C.M.; Komisar, J.R.; Mourad, A.; Kincaid, B.R. COVID-19-associated brief psychotic disorder. *BMJ Case Rep.* **2020**, *13*, e236940. [[CrossRef](#)]
124. Druss, B.G. Addressing the COVID-19 pandemic in populations with serious mental illness. *JAMA Psychiatry* **2020**, *77*, 891–892. [[CrossRef](#)] [[PubMed](#)]
125. Steinman, G. COVID-19 and autism. *Med. Hypotheses* **2020**, *142*, 109797. [[CrossRef](#)]
126. Baig, A.M. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. *J. Med. Virol.* **2020**, *93*, 2555–2556. [[CrossRef](#)]
127. Moreno-Perez, O.; Merino, E.; Leon-Ramirez, J.M.; Andres, M.; Ramos, J.M.; renas-Jimenez, J.; Asensio, S.; Sanchez, R.; Ruiz-Torregrosa, P.; Galan, I. Post-acute COVID-19 Syndrome. Incidence and risk factors: A Mediterranean cohort study. *J. Infect.* **2021**, *82*, 378–383. [[CrossRef](#)]
128. Nalbandian, A.; Sehgal, K.; Gupta, A.; Madhavan, M.V.; McGroder, C.; Stevens, J.S.; Cook, J.R.; Nordvig, A.S.; Shalev, D.; Sehrawat, T.S.; et al. Post-acute COVID-19 syndrome. *Nat. Med.* **2021**, *27*, 601–615. [[CrossRef](#)]
129. Montagne, A.; Nation, D.A.; Sagare, A.P.; Barisano, G.; Sweeney, M.D.; Chakhoyan, A.; Pachicano, M.; Joe, E.; Nelson, A.R.; D’Orazio, L.M.; et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature* **2020**, *581*, 71–76. [[CrossRef](#)] [[PubMed](#)]
130. Baig, A.M. Deleterious outcomes in long-hauler COVID-19: The effects of SARS-CoV-2 on the CNS in chronic COVID syndrome. *ACS Chem. Neurosci.* **2020**, *11*, 4017–4020. [[CrossRef](#)] [[PubMed](#)]
131. Huang, C.; Huang, L.; Wang, Y.; Li, X.; Ren, L.; Gu, X.; Kang, L.; Guo, L.; Liu, M.; Zhou, X.; et al. 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. *Lancet* **2021**, *397*, 220–232. [[CrossRef](#)]
132. Higgins, V.; Sohaei, D.; Diamandis, E.P.; Prassas, I. COVID-19: From an acute to chronic disease? Potential long-term health consequences. *Crit. Rev. Clin. Lab. Sci.* **2020**, *58*, 297–310. [[CrossRef](#)]
133. Townsend, L.; Dyer, A.H.; Jones, K.; Dunne, J.; Mooney, A.; Gaffney, F.; O’Connor, L.; Leavy, D.; O’Brien, K.; Dowds, J. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS ONE* **2020**, *15*, e0240784. [[CrossRef](#)]
134. Theoharides, T.C. Stress, inflammation, and autoimmunity: The 3 modern erinyes. *Clin. Ther.* **2020**, *42*, 742–744. [[CrossRef](#)] [[PubMed](#)]
135. Theoharides, T.C. The impact of psychological stress on mast cells. *Ann. Allergy Asthma Immunol. Off. Publ. Am. Coll. Allergy Asthma Immunol.* **2020**, *125*, 388–392. [[CrossRef](#)]
136. Keller, F.; Persico, A.M. The neurobiological context of autism. *Mol. Neurobiol.* **2003**, *28*, 1–22. [[CrossRef](#)]
137. El-Ansary, A.; Al-Ayadhi, L. Neuroinflammation in autism spectrum disorders. *J. Neuroinflamm.* **2012**, *9*, 265. [[CrossRef](#)] [[PubMed](#)]
138. Young, A.M.; Chakrabarti, B.; Roberts, D.; Lai, M.C.; Suckling, J.; Baron-Cohen, S. From molecules to neural morphology: Understanding neuroinflammation in autism spectrum condition. *Mol. Autism* **2016**, *7*, 9. [[CrossRef](#)]
139. Prata, J.; Machado, A.S.; von Doellinger, O.; Almeida, M.I.; Barbosa, M.A.; Coelho, R.; Santos, S.G. The contribution of inflammation to autism spectrum disorders: Recent clinical evidence. *Methods Mol. Biol.* **2019**, *2011*, 493–510.
140. Platt, M.P.; Agalliu, D.; Cutforth, T. Hello from the other side: How autoantibodies circumvent the blood-brain barrier in autoimmune encephalitis. *Front. Immunol.* **2017**, *8*, 442. [[CrossRef](#)]

141. Theoharides, T.C.; Angelidou, A.; Alysandratos, K.D.; Zhang, B.; Asadi, S.; Francis, K.; Toniato, E.; Kalogeromitros, D. Mast cell activation and autism. *Biochim. Biophys. Acta* **2012**, *1822*, 34–41. [[CrossRef](#)]
142. Theoharides, T.C.; Donelan, J.M.; Papadopoulou, N.; Cao, J.; Kempuraj, D.; Conti, P. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol. Sci.* **2004**, *25*, 563–568. [[CrossRef](#)] [[PubMed](#)]
143. Pedersen, J.M.; Mortensen, E.L.; Christensen, D.S.; Rozing, M.; Brunsgaard, H.; Meincke, R.H.; Petersen, G.L.; Lund, R. Prenatal and early postnatal stress and later life inflammation. *Psychoneuroendocrinology* **2018**, *88*, 158–166. [[CrossRef](#)]
144. Marsland, A.L.; Walsh, C.; Lockwood, K.; John-Henderson, N.A. The effects of acute psychological stress on circulating and stimulated inflammatory markers: A systematic review and meta-analysis. *Brain Behav. Immun.* **2017**, *64*, 208–219. [[CrossRef](#)] [[PubMed](#)]
145. Rudolph, M.D.; Graham, A.M.; Feczko, E.; Miranda-Dominguez, O.; Rasmussen, J.M.; Nardos, R.; Entringer, S.; Wadhwa, P.D.; Buss, C.; Fair, D.A. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. *Nat. Neurosci.* **2018**, *21*, 765–772. [[CrossRef](#)]
146. Huang, M.; Pang, X.; Karalis, K.; Theoharides, T.C. Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in Apolipoprotein E knockout mice. *Cardiovasc. Res.* **2003**, *59*, 241–249. [[CrossRef](#)]
147. Desai, A.; Jung, M.Y.; Olivera, A.; Gilfillan, A.M.; Prussin, C.; Kirshenbaum, A.S.; Beaven, M.A.; Metcalfe, D.D. IL-6 promotes an increase in human mast cell numbers and reactivity through suppression of suppressor of cytokine signaling 3. *J. Allergy Clin. Immunol.* **2016**, *137*, 1863–1871. [[CrossRef](#)]
148. O’Keeffe, G.W. A new role for placental IL-6 signalling in determining neurodevelopmental outcome. *Brain Behav. Immun.* **2017**, *62*, 9–10. [[CrossRef](#)] [[PubMed](#)]
149. Theoharides, T.C.; Konstantinidou, A. Corticotropin-releasing hormone and the blood-brain-barrier. *Front. Biosci.* **2007**, *12*, 1615–1628. [[CrossRef](#)] [[PubMed](#)]
150. Fiorentino, M.; Sapone, A.; Senger, S.; Camhi, S.S.; Kadzielski, S.M.; Buie, T.M.; Kelly, D.L.; Cascella, N.; Fasano, A. Blood-brain barrier and intestinal epithelial barrier alterations in autism spectrum disorders. *Mol. Autism* **2016**, *7*, 49. [[CrossRef](#)]
151. Kempuraj, D.; Papadopoulou, N.G.; Lytinas, M.; Huang, M.; Kandere-Grzybowska, K.; Madhappan, B.; Boucher, W.; Christodoulou, S.; Athanassiou, A.; Theoharides, T.C. Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells. *Endocrinology* **2004**, *145*, 43–48. [[CrossRef](#)]
152. Mastorakos, G.; Chrousos, G.P.; Weber, J.S. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J. Clin. Endocrinol. Metab.* **1993**, *77*, 1690–1694.
153. Stolp, H.B.; Dziegielewska, K.M.; Ek, C.J.; Habgood, M.D.; Lane, M.A.; Potter, A.M.; Saunders, N.R. Breakdown of the blood-brain barrier to proteins in white matter of the developing brain following systemic inflammation. *Cell Tissue Res.* **2005**, *320*, 369–378. [[CrossRef](#)]
154. Esposito, P.; Chandler, N.; Kandere-Grzybowska, K.; Basu, S.; Jacobson, S.; Connolly, R.; Tutor, D.; Theoharides, T.C. Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood-brain-barrier permeability induced by acute stress. *J. Pharmacol. Exp. Ther.* **2002**, *303*, 1061–1066. [[CrossRef](#)]
155. Theoharides, T.C.; Doyle, R. Autism, gut-blood-brain barrier and mast cells. *J. Clin. Psychopharm.* **2008**, *28*, 479–483. [[CrossRef](#)] [[PubMed](#)]
156. Rozniecki, J.J.; Sahagian, G.G.; Kempuraj, D.; Tao, K.; Jacobson, S.; Zhang, B.; Theoharides, T.C. Brain metastases of mouse mammary adenocarcinoma is increased by acute stress. *Brain Res.* **2010**, *1366*, 204–210. [[CrossRef](#)] [[PubMed](#)]
157. Theoharides, T.C.; Rozniecki, J.J.; Sahagian, G.; Jacobson, S.; Kempuraj, D.; Conti, P.; Kalogeromitros, D. Impact of stress and mast cells on brain metastases. *J. Neuroimmunol.* **2008**, *205*, 1–7. [[CrossRef](#)] [[PubMed](#)]
158. Saunders, N.R. Ontogeny of the blood-brain barrier. *Exp. Eye Res.* **1977**, *25*, 523–550. [[CrossRef](#)]
159. Saunders, N.R.; Liddel, S.A.; Dziegielewska, K.M. Barrier mechanisms in the developing brain. *Front Pharmacol.* **2012**, *3*, 46. [[CrossRef](#)]
160. Bueno, D.; Parvas, M.; Hermelo, I.; Garcia-Fernandez, J. Embryonic blood-cerebrospinal fluid barrier formation and function. *Front. Neurosci.* **2014**, *8*, 343. [[CrossRef](#)]
161. Saunders, N.R.; Dziegielewska, K.M.; Mollgard, K.; Habgood, M.D. Recent developments in understanding barrier mechanisms in the developing brain: Drugs and drug transporters in pregnancy, susceptibility or protection in the fetal brain? *Annu. Rev. Pharmacol. Toxicol.* **2019**, *59*, 487–505. [[CrossRef](#)] [[PubMed](#)]
162. Koehn, L.; Habgood, M.; Huang, Y.; Dziegielewska, K.; Saunders, N. Determinants of drug entry into the developing brain. *F1000 Res.* **2019**, *8*, 1372. [[CrossRef](#)] [[PubMed](#)]
163. Ji, Y.; Azuine, R.E.; Zhang, Y.; Hou, W.; Hong, X.; Wang, G.; Riley, A.; Pearson, C.; Zuckerman, B.; Wang, X. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry* **2019**, *77*, 180–189. [[CrossRef](#)] [[PubMed](#)]
164. Li, Z.; Ge, J.; Yang, M.; Feng, J.; Qiao, M.; Jiang, R.; Bi, J.; Zhan, G.; Xu, X.; Wang, L.; et al. Vicarious traumatization in the general public, members, and non-members of medical teams aiding in COVID-19 control. *Brain Behav. Immun.* **2020**, *88*, 916–919. [[CrossRef](#)]
165. Zhang, K.; Zhou, X.; Liu, H.; Hashimoto, K. Treatment concerns for psychiatric symptoms in patients with COVID-19 with or without psychiatric disorders. *Br. J. Psychiatry* **2020**, *217*, 351. [[CrossRef](#)]

166. Walton, M.; Murray, E.; Christian, M.D. Mental health care for medical staff and affiliated healthcare workers during the COVID-19 pandemic. *Eur. Heart J. Acute Cardiovasc. Care* **2020**, *9*, 241–247. [[CrossRef](#)]
167. Ren, Y.; Zhou, Y.; Qian, W.; Li, Z.; Liu, Z.; Wang, R.; Qi, L.; Yang, J.; Song, X.; Zeng, L.; et al. Letter to the Editor “A longitudinal study on the mental health of general population during the COVID-19 epidemic in China”. *Brain Behav. Immunol.* **2020**, *87*, 132–133. [[CrossRef](#)]
168. Loades, M.E.; Chatburn, E.; Higson-Sweeney, N.; Reynolds, S.; Shafran, R.; Brigden, A.; Linney, C.; McManus, M.N.; Borwick, C.; Crawley, E. Rapid systematic review: The impact of social isolation and loneliness on the mental health of children and adolescents in the context of COVID-19. *J. Am. Acad. Child Adolesc. Psychiatry* **2020**, *59*, 1218–1239. [[CrossRef](#)]
169. Peters, J.L.; Cohen, S.; Staudenmayer, J.; Hosen, J.; Platts-Mills, T.A.; Wright, R.J. Prenatal negative life events increases cord blood IgE: Interactions with dust mite allergen and maternal atopy. *Allergy* **2012**, *67*, 545–551. [[CrossRef](#)]
170. Wang, I.J.; Wen, H.J.; Chiang, T.L.; Lin, S.J.; Guo, Y.L. Maternal psychological problems increased the risk of childhood atopic dermatitis 1. *Pediatr. Allergy Immunol.* **2016**, *27*, 169–176. [[CrossRef](#)]
171. Andersson, N.W.; Hansen, M.V.; Larsen, A.D.; Hougaard, K.S.; Kolstad, H.A.; Schlunssen, V. Prenatal maternal stress and atopic diseases in the child: A systematic review of observational human studies. *Allergy* **2016**, *71*, 15–26. [[CrossRef](#)] [[PubMed](#)]
172. Medsker, B.; Forno, E.; Simhan, H.; Celedon, J.C. Prenatal stress, prematurity, and asthma. *Obstet. Gynecol. Surv.* **2015**, *70*, 773–779. [[CrossRef](#)] [[PubMed](#)]
173. Rosa, M.J.; Lee, A.G.; Wright, R.J. Evidence establishing a link between prenatal and early-life stress and asthma development. *Curr. Opin. Allergy Clin. Immunol.* **2018**, *18*, 148–158. [[CrossRef](#)] [[PubMed](#)]
174. Van de Loo, K.F.; van Gelder, M.M.; Roukema, J.; Roeleveld, N.; Merkus, P.J.; Verhaak, C.M. Prenatal maternal psychological stress and childhood asthma and wheezing: A meta-analysis. *Eur. Respir. J.* **2016**, *47*, 133–146. [[CrossRef](#)]
175. Postorino, V.; Kerns, C.M.; Vivanti, G.; Bradshaw, J.; Siracusano, M.; Mazzone, L. Anxiety disorders and obsessive-compulsive disorder in individuals with autism spectrum disorder. *Curr. Psychiatry Rep.* **2017**, *19*, 92. [[CrossRef](#)]
176. Cai, R.Y.; Richdale, A.L.; Uljarevic, M.; Dissanayake, C.; Samson, A.C. Emotion regulation in autism spectrum disorder: Where we are and where we need to go. *Autism Res.* **2018**, *11*, 962–978. [[CrossRef](#)]
177. Ye, Q.; Wang, B.; Mao, J. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *J. Infect.* **2020**, *80*, 607–613. [[CrossRef](#)] [[PubMed](#)]
178. Chen, G.; Wu, D.; Guo, W.; Cao, Y.; Huang, D.; Wang, H.; Wang, T.; Zhang, X.; Chen, H.; Yu, H.; et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Investig.* **2020**, *130*, 2620–2629. [[CrossRef](#)]
179. Conti, P.; Ronconi, G.; Caraffa, A.; Gallenga, C.E.; Ross, R.; Frydas, I.; Kritas, S.K. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): Anti-inflammatory strategies. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 327–331.
180. Giamarellos-Bourboulis, E.J.; Netea, M.G.; Rovina, N.; Akinosoglou, K.; Antoniadou, A.; Antonakos, N.; Damoraki, G.; Gkavogianni, T.; Adami, M.-E.; Katsaounou, P.; et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host. Microbe* **2020**, *27*, 992–1000. [[CrossRef](#)]
181. Tang, Y.; Liu, J.; Zhang, D.; Xu, Z.; Ji, J.; Wen, C. Cytokine storm in COVID-19: The current evidence and treatment strategies. *Front. Immunol.* **2020**, *11*, 1708. [[CrossRef](#)]
182. Paces, J.; Strizova, Z.; Smrz, D.; Cerny, J. COVID-19 and the immune system. *Physiol. Res.* **2020**, *69*, 379–388. [[CrossRef](#)]
183. Ragab, D.; Salah, E.H.; Taeimah, M.; Khattab, R.; Salem, R. The COVID-19 cytokine storm; What we know so far. *Front. Immunol.* **2020**, *11*, 1446. [[CrossRef](#)]
184. Brodin, P. Immune determinants of COVID-19 disease presentation and severity. *Nat. Med.* **2021**, *27*, 28–33. [[CrossRef](#)] [[PubMed](#)]
185. Canna, S.W.; Cron, R.Q. Highways to hell: Mechanism-based management of cytokine storm syndromes. *J. Allergy Clin. Immunol.* **2020**, *146*, 949–959. [[CrossRef](#)]
186. Herold, T.; Jurinovic, V.; Arnreich, C.; Lipworth, B.J.; Hellmuth, J.C.; von Bergwelt-Baildon, M.; Klein, M.; Weinberger, T. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J. Allergy Clin. Immunol.* **2020**, *146*, 128–136. [[CrossRef](#)] [[PubMed](#)]
187. Han, H.; Ma, Q.; Li, C.; Liu, R.; Zhao, L.; Wang, W.; Zhang, P.; Liu, X.; Gao, G.; Liu, F. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg. Microbes. Infect.* **2020**, *9*, 1123–1130. [[CrossRef](#)]
188. Mazzoni, A.; Salvati, L.; Maggi, L.; Capone, M.; Vanni, A.; Spinicci, M.; Mencarini, J.; Caporale, R.; Peruzzi, B.; Antonelli, A.; et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. *J. Clin. Investig.* **2020**, *130*, 4694–4703. [[CrossRef](#)]
189. Liu, F.; Li, L.; Xu, M.; Wu, J.; Luo, D.; Zhu, Y.; Li, B.; Song, X.; Zhou, X. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. *J. Clin. Virol.* **2020**, *127*, 104370. [[CrossRef](#)] [[PubMed](#)]
190. Copaescu, A.; Smibert, O.; Gibson, A.; Phillips, E.J.; Trubiano, J.A. The role of IL-6 and other mediators in the cytokine storm associated with SARS-CoV-2 infection. *J. Allergy Clin. Immunol.* **2020**, *146*, 518–534. [[CrossRef](#)] [[PubMed](#)]
191. Conti, P.; Caraffa, A.; Gallenga, C.E.; Ross, R.; Kritas, S.K.; Frydas, I.; Younes, A.; Ronconi, G. Coronavirus-19 (SARS-CoV-2) induces acute severe lung inflammation via IL-1 causing cytokine storm in COVID-19: A promising inhibitory strategy. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 1971–1975.
192. Kritas, S.K.; Ronconi, G.; Caraffa, A.; Gallenga, C.E.; Ross, R.; Conti, P. Mast cells contribute to coronavirus-induced inflammation: New anti-inflammatory strategy. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 9–14.

193. Theoharides, T.C. COVID-19, pulmonary mast cells, cytokine storms, and beneficial actions of luteolin. *Biofactors* **2020**, *46*, 306–308. [[CrossRef](#)] [[PubMed](#)]
194. Afrin, L.B.; Weinstock, L.B.; Molderings, G.J. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. *Int. J. Infect. Dis.* **2020**, *100*, 327–332. [[CrossRef](#)] [[PubMed](#)]
195. Theoharides, T.C. Potential association of mast cells with COVID-19. *Ann. Allergy Asthma Immunol.* **2020**, *126*, 217–218. [[CrossRef](#)] [[PubMed](#)]
196. Motta, J.D.S., Jr.; Miggiolaro, A.F.R.D.S.; Nagashima, S.; de Paula, C.B.V.; Baena, C.P.; Scharfstein, J.; de Noronha, L. Mast cells in alveolar septa of COVID-19 patients: A pathogenic pathway that may link interstitial edema to immunothrombosis. *Front. Immunol.* **2020**, *11*, 574862. [[CrossRef](#)]
197. Theoharides, T.C.; Valent, P.; Akin, C. Mast cells, mastocytosis, and related disorders. *N. Engl. J. Med.* **2015**, *373*, 163–172. [[CrossRef](#)]
198. Fombonne, E. Epidemiology of pervasive developmental disorders. *Pediatr. Res.* **2009**, *65*, 591–598. [[CrossRef](#)]
199. McPartland, J.; Volkmar, F.R. Autism and related disorders. *Handb. Clin. Neurol.* **2012**, *106*, 407–418. [[PubMed](#)]
200. Chang, H.Y.; Seo, J.H.; Kim, H.Y.; Kwon, J.W.; Kim, B.J.; Kim, H.B.; Lee, S.Y.; Jang, G.C.; Song, D.J.; Kim, W.K. Allergic diseases in preschoolers are associated with psychological and behavioural problems. *Allergy Asthma Immunol. Res.* **2013**, *5*, 315–321. [[CrossRef](#)]
201. Jyonouchi, H. Food allergy and autism spectrum disorders: Is there a link? *Curr. Allergy Asthma Rep.* **2009**, *9*, 194–201. [[CrossRef](#)] [[PubMed](#)]
202. Li, H.; Liu, H.; Chen, X.; Zhang, J.; Tong, G.; Sun, Y. Association of food hypersensitivity in children with the risk of autism spectrum disorder: A meta-analysis. *Eur. J. Pediatr.* **2021**, *180*, 999–1008. [[CrossRef](#)] [[PubMed](#)]
203. Xu, G.; Snetselaar, L.G.; Jing, J.; Liu, B.; Strathearn, L.; Bao, W. Association of food allergy and other allergic conditions with autism spectrum disorder in children. *JAMA Netw. Open* **2018**, *1*, e180279. [[CrossRef](#)] [[PubMed](#)]
204. Tan, Y.; Thomas, S.; Lee, B.K. Parent-reported prevalence of food allergies in children with autism spectrum disorder: National health interview survey, 2011–2015. *Autism Res.* **2019**, *12*, 802–805. [[CrossRef](#)]
205. Peretti, S.; Mariano, M.; Mazzocchetti, C.; Mazza, M.; Pino, M.C.; Verrotti Di, P.A.; Valenti, M. Diet: The keystone of autism spectrum disorder? *Nutr. Neurosci.* **2019**, *22*, 825–839. [[CrossRef](#)]
206. Mostafa, G.A.; Al-Ayadhi, L.Y. The possible relationship between allergic manifestations and elevated serum levels of brain specific auto-antibodies in autistic children. *J. Neuroimmunol.* **2013**, *261*, 77–81. [[CrossRef](#)]
207. Ravn, N.H.; Halling, A.S.; Berkowitz, A.G.; Rinnov, M.R.; Silverberg, J.I.; Egeberg, A.; Thyssen, J.P. How does parental history of atopic disease predict the risk of atopic dermatitis in a child? A systematic review and meta-analysis. *J. Allergy Clin. Immunol.* **2020**, *145*, 1182–1193. [[CrossRef](#)]
208. Estes, M.L.; McAllister, A.K. Maternal immune activation: Implications for neuropsychiatric disorders. *Science* **2016**, *353*, 772–777. [[CrossRef](#)] [[PubMed](#)]
209. Zerbo, O.; Leong, A.; Barcellos, L.; Bernal, P.; Fireman, B.; Croen, L.A. Immune mediated conditions in autism spectrum disorders. *Brain Behav. Immun.* **2015**, *46*, 232–236. [[CrossRef](#)]
210. Comi, A.M.; Zimmerman, A.W.; Frye, V.H.; Law, P.A.; Peeden, J.N. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J. Child Neurol.* **1999**, *14*, 388–394. [[CrossRef](#)]
211. Jarmołowska, B.; Bukała, M.; Fiedorowicz, E.; Cieślińska, A.; Kordulewska, N.K.; Moszyńska, M.; Świątecki, A.; Kostyra, E. Role of Milk-Derived Opioid Peptides and Proline Dipeptidyl Peptidase-4 in Autism Spectrum Disorders. *Nutrients* **2019**, *11*, 87. [[CrossRef](#)]
212. Zhou, L.; Chen, L.; Li, X.; Li, T.; Dong, Z.; Wang, Y.T. Food allergy induces alteration in brain inflammatory status and cognitive impairments. *Behav. Brain Res.* **2019**, *364*, 374–382. [[CrossRef](#)] [[PubMed](#)]
213. Msallam, R.; Balla, J.; Rathore, A.P.S.; Kared, H.; Malleret, B.; Saron, W.A.A.; Liu, Z.; Hang, J.W.; Dutertre, C.A.; Larbi, A.; et al. Fetal mast cells mediate postnatal allergic responses dependent on maternal IgE. *Science* **2020**, *370*, 941–950. [[CrossRef](#)]
214. Lenz, K.M.; Pickett, L.A.; Wright, C.L.; Davis, K.T.; Joshi, A.; McCarthy, M.M. Mast cells in the developing brain determine adult sexual behavior. *J. Neurosci.* **2018**, *38*, 8044–8059. [[CrossRef](#)]
215. Theoharides, T.C.; Petra, A.I.; Taracanova, A.; Panagiotidou, S.; Conti, P. Targeting IL-33 in autoimmunity and inflammation. *J. Pharmacol. Exp. Ther.* **2015**, *354*, 24–31. [[CrossRef](#)]
216. Theoharides, T.C.; Leeman, S.E. Effect of IL-33 on de novo synthesized mediators from human mast cells. *J. Allergy Clin. Immunol.* **2019**, *143*, 451. [[CrossRef](#)] [[PubMed](#)]
217. Zhang, X.; Dong, H.; Li, N.; Zhang, S.; Sun, J.; Zhang, S.; Qian, Y. Activated brain mast cells contribute to postoperative cognitive dysfunction by evoking microglia activation and neuronal apoptosis. *J. Neuroinflamm.* **2016**, *13*, 127. [[CrossRef](#)]
218. Gurish, M.F.; Austen, K.F. Developmental origin and functional specialization of mast cell subsets. *Immunity* **2012**, *37*, 25–33. [[CrossRef](#)]
219. Olivera, A.; Beaven, M.A.; Metcalfe, D.D. Mast cells signal their importance in health and disease. *J. Allergy Clin. Immunol.* **2018**, *142*, 381–393. [[CrossRef](#)]
220. Galli, S.J.; Tsai, M.; Piliponsky, A.M. The development of allergic inflammation. *Nature* **2008**, *454*, 445–454. [[CrossRef](#)] [[PubMed](#)]
221. Theoharides, T.C.; Alysandratos, K.D.; Angelidou, A.; Delivanis, D.A.; Sismanopoulos, N.; Zhang, B.; Asadi, S.; Vasiadi, M.; Weng, Z.; Miniati, A.; et al. Mast cells and inflammation. *Biochim. Biophys. Acta* **2012**, *1822*, 21–33. [[CrossRef](#)]

222. Mukai, K.; Tsai, M.; Saito, H.; Galli, S.J. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol. Rev.* **2018**, *282*, 121–150. [[CrossRef](#)] [[PubMed](#)]
223. Theoharides, T.C.; Alysandratos, K.D.; Angelidou, A.; Delivanis, D.A.; Sismanopoulos, N.; Zhang, B.; Asadi, S.; Vasiadi, M.; Weng, Z.; Miniati, A. Interleukin-1 family cytokines and mast cells: Activation and inhibition. *J. Biol. Regul. Homeost. Agents* **2019**, *33*, 1–6.
224. Taracanova, A.; Tsilioni, I.; Conti, P.; Norwitz, E.R.; Leeman, S.E.; Theoharides, T.C. Substance P and IL-33 administered together stimulate a marked secretion of IL-1beta from human mast cells, inhibited by methoxyluteolin. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, e9381–e9390. [[CrossRef](#)]
225. Kandere-Grzybowska, K.; Letourneau, R.; Kempuraj, D.; Donelan, J.; Poplawski, S.; Boucher, W.; Athanassiou, A.; Theoharides, T.C. IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells. *J. Immunol.* **2003**, *171*, 4830–4836. [[CrossRef](#)] [[PubMed](#)]
226. Taracanova, A.; Alevizos, M.; Karagkouni, A.; Weng, Z.; Norwitz, E.; Conti, P.; Leeman, S.E.; Theoharides, T.C. SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, e4002–e4009. [[CrossRef](#)] [[PubMed](#)]
227. Rozniecki, J.J.; Dimitriadou, V.; Lambracht-Hall, M.; Pang, X.; Theoharides, T.C. Morphological and functional demonstration of rat dura mast cell-neuron interactions in vitro and in vivo. *Brain Res.* **1999**, *849*, 1–15. [[CrossRef](#)]
228. Polyzoidis, S.; Koletsa, T.; Panagiotidou, S.; Ashkan, K.; Theoharides, T.C. Mast cells in meningiomas and brain inflammation. *J. Neuroinflammation* **2015**, *12*, 170. [[CrossRef](#)] [[PubMed](#)]
229. Pang, X.; Letourneau, R.; Rozniecki, J.J.; Wang, L.; Theoharides, T.C. Definitive characterization of rat hypothalamic mast cells. *Neuroscience* **1996**, *73*, 889–902. [[CrossRef](#)]
230. Kandere-Grzybowska, K.; Gheorghe, D.; Priller, J.; Esposito, P.; Huang, M.; Gerard, N.; Theoharides, T.C. Stress-induced dura vascular permeability does not develop in mast cell-deficient and neurokinin-1 receptor knockout mice. *Brain Res.* **2003**, *980*, 213–220. [[CrossRef](#)]
231. Matsumoto, I.; Inoue, Y.; Shimada, T.; Aikawa, T. Brain mast cells act as an immune gate to the hypothalamic-pituitary-adrenal axis in dogs. *J. Exp. Med.* **2001**, *194*, 71–78. [[CrossRef](#)] [[PubMed](#)]
232. Bugajski, A.J.; Chlap, Z.; Gadek-Michalska, A.; Borycz, J.; Bugajski, J. Degranulation and decrease in histamine levels of thalamic mast cells coincides with corticosterone secretion induced by compound 48/80. *Inflamm. Res.* **1995**, *44*, S50–S51. [[CrossRef](#)] [[PubMed](#)]
233. Kalogeromitros, D.; Syrigou, E.I.; Makris, M.; Kempuraj, D.; Stavrianeas, N.G.; Vasiadi, M.; Theoharides, T.C. Nasal provocation of patients with allergic rhinitis and the hypothalamic-pituitary-adrenal axis. *Ann. Allergy Asthma Immunol.* **2007**, *98*, 269–273. [[CrossRef](#)]
234. Scaccianoce, S.; Lombardo, K.; Nicolai, R.; Affricano, D.; Angelucci, L. Studies on the involvement of histamine in the hypothalamic-pituitary-adrenal axis activation induced by nerve growth factor. *Life Sci.* **2000**, *67*, 3143–3152. [[CrossRef](#)]
235. Alysandratos, K.; Asadi, S.; Angelidou, A.; Zhang, B.; Sismanopoulos, N.; Yang, H.; Critchfield, A.; Theoharides, T.C. Neurotensin and CRH interactions augment human mast cell activation. *PLoS ONE* **2012**, *7*, e48934. [[CrossRef](#)] [[PubMed](#)]
236. Asadi, S.; Alysandratos, K.-D.; Angelidou, A.; Miniati, A.; Sismanopoulos, N.; Vasiadi, M.; Zhang, B.; Kalogeromitros, D.; Theoharides, T.C. Substance P (SP) induces expression of functional corticotropin-releasing hormone receptor-1 (CRHR-1) in human mast cells. *J. Invest. Dermatol.* **2012**, *132*, 324–329. [[CrossRef](#)]
237. Marshall, J.S.; Portales-Cervantes, L.; Leong, E. Mast cell responses to viruses and pathogen products. *Int. J. Mol. Sci.* **2019**, *20*, 4241. [[CrossRef](#)]
238. Ziegler, C.G.K.; Allon, S.J.; Nyquist, S.K.; Mbanjo, I.M.; Miao, V.N.; Tzouanas, C.N.; Cao, Y.; Yousif, A.S.; Bals, J.; Hauser, B.M. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell* **2020**, *181*, 1016–1035. [[CrossRef](#)]
239. Dietrich, N.; Rohde, M.; Geffers, R.; Kroger, A.; Hauser, H.; Weiss, S.; Gekara, N.O. Mast cells elicit proinflammatory but not type I interferon responses upon activation of TLRs by bacteria. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 8748–8753. [[CrossRef](#)]
240. Bawazeer, M.A.; Theoharides, T.C. IL-33 stimulates human mast cell release of CCL5 and CCL2 via MAPK and NF-kappaB, inhibited by methoxyluteolin. *Eur. J. Pharmacol.* **2019**, *865*, 172760. [[CrossRef](#)]
241. Saluja, R.; Khan, M.; Church, M.K.; Maurer, M. The role of IL-33 and mast cells in allergy and inflammation. *Clin. Transl. Allergy* **2015**, *5*, 33. [[CrossRef](#)] [[PubMed](#)]
242. Conti, P.; Caraffa, A.; Tete, G.; Gallenga, C.E.; Ross, R.; Kritas, S.K.; Frydas, I.; Younes, A.; Di, E.P.; Ronconi, G. Mast cells activated by SARS-CoV-2 release histamine which increases IL-1 levels causing cytokine storm and inflammatory reaction in COVID-19. *J. Biol. Regul. Homeost. Agents* **2020**, *34*, 1629–1632.
243. Zhang, B.; Asadi, S.; Weng, Z.; Sismanopoulos, N.; Theoharides, T.C. Stimulated human mast cells secrete mitochondrial components that have autocrine and paracrine inflammatory actions. *PLoS ONE* **2012**, *7*, e49767. [[CrossRef](#)]
244. Collins, L.V.; Hajizadeh, S.; Holme, E.; Jonsson, I.M.; Tarkowski, A. Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. *J. Leukoc. Biol.* **2004**, *75*, 995–1000. [[CrossRef](#)] [[PubMed](#)]
245. Sun, S.; Sursal, T.; Adibnia, Y.; Zhao, C.; Zheng, Y.; Li, H.; Otterbein, L.E.; Hauser, C.J.; Itagaki, K. Mitochondrial DAMPs increase endothelial permeability through neutrophil dependent and independent pathways. *PLoS ONE* **2013**, *8*, e59989. [[CrossRef](#)] [[PubMed](#)]

246. Zhang, B.; Angelidou, A.; Alysandratos, K.D.; Vasiadi, M.; Francis, K.; Asadi, S.; Theoharides, A.; Sideri, K.; Lykouras, L.; Kalogeromitros, D. Mitochondrial DNA and anti-mitochondrial antibodies in serum of autistic children. *J. Neuroinflammation* **2010**, *7*, 80. [[CrossRef](#)]
247. Frye, R.E.; Cakir, J.; Rose, S.; Palmer, R.F.; Austin, C.; Curtin, P.; Arora, M. Mitochondria may mediate prenatal environmental influences in autism spectrum disorder. *J. Pers. Med.* **2021**, *11*, 218. [[CrossRef](#)] [[PubMed](#)]
248. Scozzi, D.; Cano, M.; Ma, L.; Zhou, D.; Zhu, J.H.; O'Halloran, J.A.; Goss, C.W.; Rauseo, A.M.; Liu, Z.; Sahu, S.K.; et al. Circulating mitochondrial DNA is an early indicator of severe illness and mortality from COVID-19. *JCI Insight* **2021**, *6*, e143299.
249. Demopoulos, C.; Antonopoulou, S.; Theoharides, T.C. COVID-19, microthromboses, inflammation, and platelet activating factor. *Biofactors* **2020**, *46*, 927–933. [[CrossRef](#)]
250. Theoharides, T.C.; Antonopoulou, S.; Demopoulos, C.A. Coronavirus 2019, microthromboses, and platelet activating factor. *Clin. Ther.* **2020**, *42*, 1850–1852. [[CrossRef](#)]
251. Damialis, A.; Gilles, S.; Sofiev, M.; Sofieva, V.; Kolek, F.; Bayr, D.; Plaza, M.P.; Leier-Wirtz, V.; Kaschuba, S.; Ziska, L.H. Higher airborne pollen concentrations correlated with increased SARS-CoV-2 infection rates, as evidenced from 31 countries across the globe. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2019034118. [[CrossRef](#)]
252. Subhramanyam, C.S.; Wang, C.; Hu, Q.; Dheen, S.T. Microglia-mediated neuroinflammation in neurodegenerative diseases. *Semin. Cell Dev. Biol.* **2019**, *94*, 112–120. [[CrossRef](#)] [[PubMed](#)]
253. Colonna, M.; Butovsky, O. Microglia function in the central nervous system during health and neurodegeneration. *Annu. Rev. Immunol.* **2017**, *35*, 441–468. [[CrossRef](#)]
254. Voet, S.; Prinz, M.; van Loo, G. Microglia in central nervous system inflammation and multiple sclerosis pathology. *Trends Mol. Med.* **2019**, *25*, 112–123. [[CrossRef](#)]
255. Perry, V.H.; Nicoll, J.A.; Holmes, C. Microglia in neurodegenerative disease. *Nat. Rev. Neurol.* **2010**, *6*, 193–201. [[CrossRef](#)]
256. Ransohoff, R.M. How neuroinflammation contributes to neurodegeneration. *Science* **2016**, *353*, 777–783. [[CrossRef](#)]
257. Hickman, S.; Izzy, S.; Sen, P.; Morsett, L.; El, K.J. Microglia in neurodegeneration. *Nat. Neurosci.* **2018**, *21*, 1359–1369. [[CrossRef](#)] [[PubMed](#)]
258. Xu, Z.X.; Kim, G.H.; Tan, J.W.; Riso, A.E.; Sun, Y.; Xu, E.Y.; Liao, G.Y.; Xu, H.; Lee, S.H.; Do, N.Y. Elevated protein synthesis in microglia causes autism-like synaptic and behavioral aberrations. *Nat. Commun.* **2020**, *11*, 1797. [[CrossRef](#)] [[PubMed](#)]
259. Patel, A.B.; Tsilioni, I.; Leeman, S.E.; Theoharides, T.C. Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, e7049–e7058. [[CrossRef](#)]
260. Vargas, G.; Medeiros Geraldo, L.H.; Gedeao, S.N.; Viana, P.M.; Regina Souza, L.F.; Carvalho Alcantara, G.F. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and glial cells: Insights and perspectives. *Brain Behav. Immun. Health* **2020**, *7*, 100127. [[CrossRef](#)]
261. Tremblay, M.E.; Madore, C.; Bordeleau, M.; Tian, L.; Verkhratsky, A. Neuropathobiology of COVID-19: The role for glia. *Front. Cell Neurosci.* **2020**, *14*, 592214. [[CrossRef](#)]
262. Lee, N.; Chan, P.K.; Ip, M.; Wong, E.; Ho, J.; Ho, C.; Cockram, C.S.; Hui, D.S. Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. *J. Clin. Virol.* **2006**, *35*, 179–184. [[CrossRef](#)]
263. Sotgiu, S.; Manca, S.; Gagliano, A.; Minutolo, A.; Melis, M.C.; Pisuttu, G.; Scoppola, C.; Bolognesi, E.; Clerici, M.; Guerini, F.R.; et al. Immune regulation of neurodevelopment at the mother-foetus interface: The case of autism. *Clin. Transl. Immunol.* **2020**, *9*, e1211. [[CrossRef](#)] [[PubMed](#)]
264. Hendriksen, E.; van Bergeijk, D.; Oosting, R.S.; Redegeld, F.A. Mast cells in neuroinflammation and brain disorders. *Neurosci. Biobehav. Rev.* **2017**, *79*, 119–133. [[CrossRef](#)]
265. Skaper, S.D.; Facci, L.; Giusti, P. Neuroinflammation, microglia and mast cells in the pathophysiology of neurocognitive disorders: A review. *CNS Neurol. Disord. Drug Targets* **2014**, *13*, 1654–1666. [[CrossRef](#)]
266. Skaper, S.D.; Facci, L.; Zusso, M.; Giusti, P. Neuroinflammation, mast cells, and glia: Dangerous liaisons. *Neuroscientist* **2017**, *23*, 478–498. [[CrossRef](#)] [[PubMed](#)]
267. Zhang, X.; Wang, Y.; Dong, H.; Xu, Y.; Zhang, S. Induction of microglial activation by mediators released from mast cells. *Cell Physiol. Biochem.* **2016**, *38*, 1520–1531. [[CrossRef](#)]
268. Theoharides, T.C.; Stewart, J.M.; Panagiotidou, S.; Melamed, I. Mast cells, brain inflammation and autism. *Eur. J. Pharmacol.* **2015**, *778*, 96–102. [[CrossRef](#)] [[PubMed](#)]
269. Dong, H.; Zhang, X.; Wang, Y.; Zhou, X.; Qian, Y.; Zhang, S. Suppression of brain mast cells degranulation inhibits microglial activation and central nervous system inflammation. *Mol. Neurobiol.* **2017**, *54*, 997–1007. [[CrossRef](#)]
270. Shaik-Dasthagirisaheb, Y.B.; Conti, P. The role of mast cells in Alzheimer's disease. *Adv. Clin. Exp. Med.* **2016**, *25*, 781–787. [[CrossRef](#)]
271. Kempuraj, D.; Mentor, S.; Thangavel, R.; Ahmed, M.E.; Selvakumar, G.P.; Raikwar, S.P.; Dubova, I.; Zaheer, S.; Iyer, S.S.; Zaheer, A. Mast cells in stress, pain, blood-brain barrier, neuroinflammation and Alzheimer's disease. *Front. Cell Neurosci.* **2019**, *13*, 54. [[CrossRef](#)]
272. Hansen, D.V.; Hanson, J.E.; Sheng, M. Microglia in Alzheimer's disease. *J. Cell Biol.* **2018**, *217*, 459–472. [[CrossRef](#)] [[PubMed](#)]
273. Hatziagelaki, E.; Adamaki, M.; Tsilioni, I.; Dimitriadis, G.; Theoharides, T.C. Myalgic encephalomyelitis/chronic fatigue syndrome-metabolic disease or disturbed homeostasis due to focal inflammation in the hypothalamus? *J. Pharmacol. Exp. Ther.* **2018**, *367*, 155–167. [[CrossRef](#)] [[PubMed](#)]

274. Breach, M.R.; Dye, C.N.; Joshi, A.; Platko, S.; Gilfarb, R.A.; Krug, A.R.; Franceschelli, D.V.; Galan, A.; Dodson, C.M.; Lenz, K.M. Maternal allergic inflammation in rats impacts the offspring perinatal neuroimmune milieu and the development of social play, locomotor behavior, and cognitive flexibility. *Brain Behav Immun.* **2021**, *95*, 269–286. [[CrossRef](#)] [[PubMed](#)]
275. Wang, W.; Ji, P.; Riopelle, R.J.; Dow, K.E. Functional expression of corticotropin-releasing hormone (CRH) receptor 1 in cultured rat microglia. *J. Neurochem.* **2002**, *80*, 287–294. [[CrossRef](#)]
276. Podlesek, A.; Komidar, L.; Kavcic, V. The relationship between perceived stress and subjective cognitive decline during the COVID-19 epidemic. *Front Psychol.* **2021**, *12*, 647971. [[CrossRef](#)]
277. Martin, S.; Dicou, E.; Vincent, J.P.; Mazella, J. Neurotensin and the neurotensin receptor-3 in microglial cells. *J. Neurosci. Res.* **2005**, *81*, 322–326. [[CrossRef](#)]
278. Angelidou, A.; Francis, K.; Vasiadi, M.; Alysandratos, K.-D.; Zhang, B.; Theoharides, A.; Lykouras, L.; Sideri, K.; Kalogeromitos, D.; Theoharides, T.C. Neurotensin is increased in serum of young children with autistic disorder. *J. Neuroinflamm.* **2010**, *7*, 48. [[CrossRef](#)] [[PubMed](#)]
279. Tsilioni, I.; Dodman, N.; Petra, A.I.; Taliou, A.; Francis, K.; Moon-Fanelli, A.; Shuster, L.; Theoharides, T.C. Elevated serum neurotensin and CRH levels in children with autistic spectrum disorders and tail-chasing Bull Terriers with a phenotype similar to autism. *Transl. Psychiatry* **2014**, *4*, e466. [[CrossRef](#)]
280. Almeshmadi, K.A.; Tsilioni, T.T.C. Increased expression of miR-155p5 in amygdala of children with Autism Spectrum Disorder. *Autism Res.* **2019**, *13*, 18–23. [[CrossRef](#)] [[PubMed](#)]
281. Tsilioni, I.; Pantazopoulos, H.; Conti, P.; Leeman, S.E.; Theoharides, T.C. IL-38 inhibits microglial inflammatory mediators and is decreased in amygdala of children with autism spectrum disorder. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 16475–16480. [[CrossRef](#)] [[PubMed](#)]
282. Jack, C.S.; Arbour, N.; Manusow, J.; Montgrain, V.; Blain, M.; McCrear, E.; Shapiro, A.; Antel, J.P. TLR signaling tailors innate immune responses in human microglia and astrocytes. *J. Immunol.* **2005**, *175*, 4320–4330. [[CrossRef](#)]
283. Murta, V.; Villarreal, A.; Ramos, A.J. Severe acute respiratory syndrome Coronavirus 2 impact on the central nervous system: Are astrocytes and microglia main players or merely bystanders? *ASN Neuro.* **2020**, *12*, 1759091420954960. [[CrossRef](#)] [[PubMed](#)]
284. Akin, C.; Valent, P.; Metcalfe, D.D. Mast cell activation syndrome: Proposed diagnostic criteria. *J. Allergy Clin. Immunol.* **2010**, *126*, 1099–1104. [[CrossRef](#)]
285. Theoharides, T.C.; Tsilioni, I.; Ren, H. Recent advances in our understanding of mast cell activation—Or should it be mast cell mediator disorders? *Expert. Rev. Clin. Immunol.* **2019**, *15*, 639–656. [[CrossRef](#)] [[PubMed](#)]
286. Enstrom, A.; Krakowiak, P.; Onore, C.; Pessah, I.N.; Hertz-Picciotto, I.; Hansen, R.L.; Van de Water, J.A.; Ashwood, P. Increased IgG4 levels in children with autism disorder. *Brain Behav. Immun.* **2009**, *23*, 389–395. [[CrossRef](#)] [[PubMed](#)]
287. Maintz, L.; Novak, N. Histamine and histamine intolerance. *Am. J. Clin. Nutr.* **2007**, *85*, 1185–1196. [[CrossRef](#)]
288. Kumar, S.; Khodoun, M.; Kettleston, E.M.; McKnight, C.; Reponen, T.; Grinshpun, S.A.; Adhikari, A. Glyphosate-rich air samples induce IL-33, TSLP and generate IL-13 dependent airway inflammation. *Toxicology* **2014**, *325*, 42–51. [[CrossRef](#)]
289. Rossignol, D.A.; Frye, R.E. A systematic review and meta-analysis of immunoglobulin g abnormalities and the therapeutic use of Intravenous Immunoglobulins (IVIg) in autism spectrum disorder. *J. Pers. Med.* **2021**, *11*, 488. [[CrossRef](#)]
290. Church, M.K. Allergy, histamine and antihistamines. *Handb. Exp. Pharmacol.* **2017**, *241*, 321–331.
291. Vasiadi, M.; Kalogeromitos, D.; Kempuraj, D.; Clemons, A.; Zhang, B.; Chliva, C.; Makris, M.; Wolfberg, A.; House, M.; Theoharides, T.C. Rupatadine inhibits proinflammatory mediator secretion from human mast cells triggered by different stimuli. *Int. Arch. Allergy Immunol.* **2010**, *151*, 38–45. [[CrossRef](#)]
292. Alevizos, M.; Karagkouni, A.; Vasiadi, M.; Sismanopoulos, N.; Makris, M.; Kalogeromitos, D.; Theoharides, T.C. Rupatadine inhibits inflammatory mediator release from human LAD2 cultured mast cells stimulated by PAF. *Ann. Allergy Asthma Immunol.* **2013**, *111*, 524–527. [[CrossRef](#)] [[PubMed](#)]
293. Siebenhaar, F.; Förtsch, A.; Krause, K.; Weller, K.; Metz, M.; Magerl, M.; Martus, P.; Church, M.K.; Maurer, M. Rupatadine improves quality of life in mastocytosis: A randomized, double-blind, placebo-controlled trial. *Allergy* **2013**, *68*, 949–952. [[CrossRef](#)] [[PubMed](#)]
294. Theoharides, T.C.; Stewart, J.M. Antihistamines and mental status. *J. Clin. Psychopharmacol.* **2016**, *36*, 195–197. [[CrossRef](#)] [[PubMed](#)]
295. Zahiruddin, S.; Basist, P.; Parveen, A.; Parveen, R.; Khan, W.; Gaurav, Ahmad, S. Ashwagandha in brain disorders: A review of recent developments. *J. Ethnopharmacol.* **2020**, *257*, 112876. [[CrossRef](#)] [[PubMed](#)]
296. Ng, Q.X.; Loke, W.; Foo, N.X.; Tan, W.J.; Chan, H.W.; Lim, D.Y.; Yeo, W.S. A systematic review of the clinical use of Withania somnifera (Ashwagandha) to ameliorate cognitive dysfunction. *Phytother. Res.* **2020**, *34*, 583–590. [[CrossRef](#)]
297. Beversdorf, D.Q.; Saklayen, S.; Higgins, K.F.; Bodner, K.E.; Kanne, S.M.; Christ, S.E. Effect of propranolol on word fluency in autism. *Cogn. Behav. Neurol.* **2011**, *24*, 11–17. [[CrossRef](#)]
298. Beversdorf, D.Q.; Saklayen, S.; Higgins, K.F.; Bodner, K.E.; Kanne, S.M.; Christ, S.E. alpha2-adrenergic agonists or stimulants for preschool-age children with attention-deficit/hyperactivity disorder. *JAMA* **2021**, *325*, 2067–2075.
299. Banas, K.; Sawchuk, B. Clonidine as a treatment of behavioural disturbances in autism spectrum disorder: A systematic literature review. *J. Can. Acad. Child Adolesc. Psychiatry* **2020**, *29*, 110–120.

300. Reichow, B.; Volkmar, F.R.; Bloch, M.H. Systematic review and meta-analysis of pharmacological treatment of the symptoms of attention-deficit/hyperactivity disorder in children with pervasive developmental disorders. *J. Autism Dev. Disord.* **2013**, *43*, 2435–2441. [[CrossRef](#)]
301. Politte, L.C.; Scahill, L.; Figueroa, J.; McCracken, J.T.; King, B.; McDougle, C.J. A randomized, placebo-controlled trial of extended-release guanfacine in children with autism spectrum disorder and ADHD symptoms: An analysis of secondary outcome measures. *Neuropsychopharmacology* **2018**, *43*, 1772–1778. [[CrossRef](#)] [[PubMed](#)]
302. Okazaki, K.; Yamamuro, K.; Iida, J.; Kishimoto, T. Guanfacine monotherapy for ADHD/ASD comorbid with Tourette syndrome: A case report. *Ann. Gen. Psychiatry* **2019**, *18*, 2. [[CrossRef](#)] [[PubMed](#)]
303. Ming, X.; Gordon, E.; Kang, N.; Wagner, G.C. Use of clonidine in children with autism spectrum disorders. *Brain Dev.* **2008**, *30*, 454–460. [[CrossRef](#)]
304. Del Giudice, E.; Rinaldi, L.; Passarotto, M.; Facchinetti, F.; D'Arrigo, A.; Guiotto, A.; Carbonare, M.D.; Battistin, L.; Leon, A. Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells. *J. Leukoc. Biol.* **2007**, *81*, 1512–1522. [[CrossRef](#)] [[PubMed](#)]
305. Caslin, H.; Kiwanuka, K.N.; Haque, T.T.; Taruselli, M.; Macknight, H.P.; Paranjape, A.; Ryan, J.J. Controlling mast cell activation and homeostasis: Work Influenced by Bill Paul that continues today. *Front. Immunol.* **2018**, *9*, 868. [[CrossRef](#)]
306. Noda, S.; Krueger, J.G.; Guttman-Yassky, E. The translational revolution and use of biologics in patients with inflammatory skin diseases. *J. Allergy Clin. Immunol.* **2015**, *135*, 324–336. [[CrossRef](#)]
307. Leonardi, C.L.; Powers, J.L.; Matheson, R.T.; Goffe, B.S.; Zitnik, R.; Wang, A.; Gottlieb, A.B. Etanercept as monotherapy in patients with psoriasis. *N. Engl. J. Med.* **2003**, *349*, 2014–2022. [[CrossRef](#)]
308. Ruzicka, T.; Mihara, R. Anti-interleukin-31 receptor antibody for atopic dermatitis. *N. Engl. J. Med.* **2017**, *376*, 2093. [[CrossRef](#)]
309. Olivieri, I.; D'Angelo, S.; Palazzi, C.; Padula, A. Treatment strategies for early psoriatic arthritis. *Expert. Opin. Pharmacother.* **2009**, *10*, 271–282. [[CrossRef](#)]
310. Heinrich, M.C.; Griffith, D.J.; Druker, B.J.; Wait, C.L.; Ott, K.A.; Zigler, A.J. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* **2000**, *96*, 925–932. [[CrossRef](#)] [[PubMed](#)]
311. Gotlib, J.; Kluijn-Nelemans, J.C.; George, T.I.; Akin, C.; Sotlar, K.; Hermine, O.; Awan, F.T.; Hexner, E.; Mauro, M.J.; Sternberg, D.W.; et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N. Engl. J. Med.* **2016**, *374*, 2530–2541. [[CrossRef](#)]
312. Finn, D.F.; Walsh, J.J. Twenty-first century mast cell stabilizers. *Br. J. Pharmacol.* **2013**, *170*, 23–37. [[CrossRef](#)]
313. Theoharides, T.C.; Sieghart, W.; Greengard, P.; Douglas, W.W. Antiallergic drug cromolyn may inhibit histamine secretion by regulating phosphorylation of a mast cell protein. *Science* **1980**, *207*, 80–82. [[CrossRef](#)]
314. Oka, T.; Kalesnikoff, J.; Starkl, P.; Tsai, M.; Galli, S.J. Evidence questioning cromolyn's effectiveness and selectivity as a 'mast cell stabilizer' in mice. *Lab. Invest.* **2012**, *92*, 1472–1482. [[CrossRef](#)] [[PubMed](#)]
315. Weng, Z.; Zhang, B.; Asadi, S.; Sismanopoulos, N.; Butcher, A.; Fu, X.; Katsarou-Katsari, A.; Antoniou, C.; Theoharides, T.C. Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans. *PLoS ONE* **2012**, *7*, e33805-k. [[CrossRef](#)]
316. Dos Santos, R.V.; Magerl, M.; Martus, P.; Zuberbier, T.; Church, M.; Escribano, L.; Maurer, M. Topical sodium cromoglycate relieves allergen- and histamine-induced dermal pruritus. *Br. J. Dermatol.* **2010**, *162*, 674–676. [[CrossRef](#)] [[PubMed](#)]
317. Weng, Z.; Patel, A.B.; Panagiotidou, S.; Theoharides, T.C. The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells. *J. Allergy Clin. Immunol.* **2015**, *135*, 1044–1052. [[CrossRef](#)] [[PubMed](#)]
318. Church, M.K.; Gradidge, C.F. Potentiation of histamine release by sodium cromoglycate. *Life Sci.* **1978**, *23*, 1899–1904. [[CrossRef](#)]
319. Kempuraj, D.; Madhappan, B.; Christodoulou, S.; Boucher, W.; Cao, J.; Papadopoulou, N.; Cetrulo, C.L.; Theoharides, T.C. Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells. *Br. J. Pharmacol.* **2005**, *145*, 934–944. [[CrossRef](#)]
320. Seelinger, G.; Merfort, I.; Schempp, C.M. Anti-oxidant, anti-inflammatory and anti-allergic activities of luteolin. *Planta Med.* **2008**, *74*, 1667–1677. [[CrossRef](#)]
321. Calis, Z.; Mogulkoc, R.; Baltaci, A.K. The roles of flavonoles/flavonoids in neurodegeneration and neuroinflammation. *Mini. Rev. Med. Chem.* **2020**, *20*, 1475–1488. [[CrossRef](#)] [[PubMed](#)]
322. Jager, A.K.; Saaby, L. Flavonoids and the CNS. *Molecules* **2011**, *16*, 1471–1485. [[CrossRef](#)]
323. Leyva-Lopez, N.; Gutierrez-Grijalva, E.P.; Ambriz-Perez, D.L.; Heredia, J.B. Flavonoids as cytokine modulators: A possible therapy for inflammation-related diseases. *Int. J. Mol. Sci.* **2016**, *17*, 921. [[CrossRef](#)]
324. Harwood, M.; Nielewska-Nikiel, B.; Borzelleca, J.F.; Flamm, G.W.; Williams, G.M.; Lines, T.C. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. *Food Chem. Toxicol.* **2007**, *45*, 2179–2205. [[CrossRef](#)]
325. Okamoto, T. Safety of quercetin for clinical application (Review). *Int. J. Mol. Med.* **2005**, *16*, 275–278. [[CrossRef](#)]
326. Andres, S.; Pevny, S.; Ziegenhagen, R.; Bakhiya, N.; Schäfer, B.; Hirsch-Ernst, K.; Lampen, A. Safety aspects of the use of quercetin as a dietary supplement. *Mol. Nutr. Food Res.* **2018**, *62*, 1700447. [[CrossRef](#)] [[PubMed](#)]
327. Xu, L.; Su, W.; Jin, J.; Chen, J.; Li, X.; Zhang, X.; Sun, M.; Sun, S.; Fan, P.; An, D.; et al. Identification of luteolin as enterovirus 71 and coxsackievirus A16 inhibitors through reporter viruses and cell viability-based screening. *Viruses* **2014**, *6*, 2778–2795. [[CrossRef](#)]

328. Fan, W.; Qian, S.; Qian, P.; Li, X. Antiviral activity of luteolin against Japanese encephalitis virus. *Virus Res.* **2016**, *220*, 112–116. [[CrossRef](#)] [[PubMed](#)]
329. Yan, H.; Ma, L.; Wang, H.; Wu, S.; Huang, H.; Gu, Z.; Jiang, J.; Li, Y. Luteolin decreases the yield of influenza A virus in vitro by interfering with the coat protein I complex expression. *J. Nat. Med.* **2019**, *73*, 487–496. [[CrossRef](#)]
330. Russo, M.; Moccia, S.; Spagnuolo, C.; Tedesco, I.; Russo, G.L. Roles of flavonoids against coronavirus infection. *Chem. Biol. Interact.* **2020**, *328*, 109211. [[CrossRef](#)]
331. Derosa, G.; Maffioli, P.; D'Angelo, A.; Di, P.F. A role for quercetin in coronavirus disease 2019 (COVID-19). *Phytother. Res.* **2020**, *35*, 1230–1236. [[CrossRef](#)]
332. Rezai-Zadeh, K.; Ehrhart, J.; Bai, Y.; Sanberg, P.R.; Bickford, P.; Tan, J.; Shytle, R.D. Apigenin and luteolin modulate microglial activation via inhibition of STAT1-induced CD40 expression. *J. Neuroinflammation* **2008**, *5*, 41. [[CrossRef](#)] [[PubMed](#)]
333. Jang, S.; Kelley, K.W.; Johnson, R.W. Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 7534–7539. [[CrossRef](#)] [[PubMed](#)]
334. Burton, M.D.; Rytch, J.L.; Amin, R.; Johnson, R.W. Dietary luteolin reduces proinflammatory microglia in the brain of senescent mice. *Rejuvenation. Res.* **2016**, *19*, 286–292. [[CrossRef](#)] [[PubMed](#)]
335. Patel, A.B.; Theoharides, T.C. Methoxyluteolin inhibits neuropeptide-stimulated proinflammatory mediator release via mTOR activation from human mast cells. *J. Pharmacol. Exp. Ther.* **2017**, *361*, 462–471. [[CrossRef](#)]
336. Dajas, F.; Rivera-Megret, F.; Blasina, F.; Arredondo, F.; Abin-Carriquiry, J.; Costa, G.; Echeverry, C.; Lafon, L.; Heizen, H.; Ferreira, M.; et al. Neuroprotection by flavonoids. *Braz. J. Med. Biol. Res.* **2003**, *36*, 1613–1620. [[CrossRef](#)]
337. Kempuraj, D.; Thangavel, R.; Kempuraj, D.D.; Ahmed, M.E.; Selvakumar, G.P.; Raikwar, S.P.; Zaheer, S.A.; Iyer, S.S.; Govindarajan, R.; Chandrasekaran, P.N. Neuroprotective effects of flavone luteolin in neuroinflammation and neurotrauma. *Biofactors* **2020**, *47*, 190–197. [[CrossRef](#)]
338. Lin, T.Y.; Lu, C.W.; Wang, S.J. Luteolin protects the hippocampus against neuron impairments induced by kainic acid in rats. *Neuro Toxicol.* **2016**, *55*, 48–57. [[CrossRef](#)]
339. Ashaari, Z.; Hassanzadeh, G.; Alizamir, T.; Yousefi, B.; Keshavarzi, Z.; Mokhtari, T. The flavone luteolin improves central nervous system disorders by different mechanisms: A review. *J. Mol. Neurosci.* **2018**, *65*, 491–506. [[CrossRef](#)]
340. Bernatoniene, J.; Kazlauskaitė, J.A.; Kopustinskiene, D.M. Pleiotropic Effects of Isoflavones in Inflammation and Chronic Degenerative Diseases. *Int J Mol Sci.* **2021**, *22*, 5656. [[CrossRef](#)]
341. Theoharides, T.C.; Conti, P.; Economu, M. Brain inflammation, neuropsychiatric disorders, and immunoendocrine effects of luteolin. *J. Clin. Psychopharmacol.* **2014**, *34*, 187–189. [[CrossRef](#)]
342. Silva Dos Santos, J.; Gonçalves Cirino, J.P.; de Oliveira Carvalho, P.; Ortega, M.M. The Pharmacological Action of Kaempferol in Central Nervous System Diseases: A Review. *Front Pharmacol.* **2021**, *11*, 565700. [[CrossRef](#)] [[PubMed](#)]
343. Devi, S.A.; Chamoli, A. Polyphenols as an effective therapeutic intervention against cognitive decline during normal and pathological brain aging. *Adv. Exp. Med. Biol.* **2020**, *1260*, 159–174. [[PubMed](#)]
344. Theoharides, T.C.; Stewart, J.M.; Hatziagelaki, E.; Kolaitis, G. Brain “fog”, inflammation and obesity: Key aspects of 2 neuropsychiatric disorders improved by luteolin. *Front. Neurosci.* **2015**, *9*, 225. [[CrossRef](#)] [[PubMed](#)]
345. Rezai-Zadeh, K.; Douglas, S.R.; Bai, Y.; Tian, J.; Hou, H.; Mori, T.; Zeng, J.; Obregon, D.; Town, T.; Tan, J. Flavonoid-mediated presenilin-1 phosphorylation reduces Alzheimer’s disease beta-amyloid production. *J. Cell Mol. Med.* **2009**, *13*, 574–588. [[CrossRef](#)]
346. Theoharides, T.C.; Cholevas, C.; Polyzoidis, K.; Politis, A. Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue. *Biofactors* **2021**, *47*, 232–241. [[CrossRef](#)]
347. Gratton, G.; Weaver, S.R.; Burley, C.V.; Low, K.A.; Maclin, E.L.; Johns, P.W.; Pham, Q.S.; Lucas, S.J.E.; Fabiani, M.; Rendeiro, C. Dietary flavanols improve cerebral cortical oxygenation and cognition in healthy adults. *Sci. Rep.* **2020**, *10*, 19409. [[CrossRef](#)]
348. Yeh, T.S.; Yuan, C.; Ascherio, A.; Rosner, B.; Willett, W.; Blacker, D. Long-term dietary flavonoid intake and subjective cognitive decline in US men and women. *Neurology* **2021**. [[CrossRef](#)]
349. Du, X.; Hill, R.A. 7,8-Dihydroxyflavone as a pro-neurotrophic treatment for neurodevelopmental disorders. *Neurochem. Int.* **2015**, *89*, 170–180. [[CrossRef](#)]
350. Xu, S.L.; Bi, C.W.; Choi, R.C.; Zhu, K.Y.; Miernisha, A.; Dong, T.T.; Tsim, K.W. Flavonoids induce the synthesis and secretion of neurotrophic factors in cultured rat astrocytes: A signaling response mediated by estrogen receptor. *Evid. Based Complement Alternat. Med.* **2013**, *2013*, 127075. [[CrossRef](#)]
351. Theoharides, T.C.; Athanassiou, M.; Panagiotidou, S.; Doyle, R. Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders. *J. Neuroimmunol.* **2015**, *279*, 33–38. [[CrossRef](#)] [[PubMed](#)]
352. Yi, L.; Li, Z.; Yuan, K.; Qu, X.; Chen, J.; Wang, G.; Zhang, H.; Luo, H.; Zhu, L.; Jiang, P.; et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. *J. Virol.* **2004**, *78*, 11334–11339. [[CrossRef](#)] [[PubMed](#)]
353. Jo, S.; Kim, S.; Shin, D.H.; Kim, M.S. Inhibition of SARS-CoV 3CL protease by flavonoids. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 145–151. [[CrossRef](#)] [[PubMed](#)]
354. Xue, G.; Gong, L.; Yuan, C.; Xu, M.; Wang, X.; Jiang, L.; Huang, M. A structural mechanism of flavonoids in inhibiting serine proteases. *Food Funct.* **2017**, *8*, 2437–2443. [[CrossRef](#)]
355. Richman, S.; Morris, M.C.; Broderick, G.; Craddock, T.J.A.; Klimas, N.G.; Fletcher, M.A. Pharmaceutical interventions in chronic fatigue syndrome: A literature-based commentary. *Clin. Ther.* **2019**, *41*, 798–805. [[CrossRef](#)] [[PubMed](#)]

356. Yi, Y.S. Regulatory roles of flavonoids on inflammasome activation during inflammatory responses. *Mol. Nutr. Food Res.* **2018**, *62*, e1800147. [[CrossRef](#)] [[PubMed](#)]
357. Fu, X.; Zhang, J.; Guo, L.; Xu, Y.; Sun, L.; Wang, S.; Feng, Y.; Gou, L.; Zhang, L.; Liu, Y. Protective role of luteolin against cognitive dysfunction induced by chronic cerebral hypoperfusion in rats. *Pharmacol. Biochem. Behav.* **2014**, *126*, 122–130. [[CrossRef](#)]
358. Theoharides, T.C. Luteolin supplements: All that glitters is not gold. *Biofactors* **2020**, *47*, 242–244. [[CrossRef](#)] [[PubMed](#)]
359. Taliou, A.; Zintzaras, E.; Lykouras, L.; Francis, K. An open-label pilot study of a formulation containing the anti-inflammatory flavonoid luteolin and its effects on behavior in children with autism spectrum disorders. *Clin. Ther.* **2013**, *35*, 592–602. [[CrossRef](#)]
360. Tsilioni, I.; Taliou, A.; Francis, K.; Theoharides, T.C. Children with Autism Spectrum Disorders, who improved with a luteolin containing dietary formulation, show reduced serum levels of TNF and IL-6. *Transl. Psychiatry* **2015**, *5*, e647. [[CrossRef](#)]
361. Beauchamp, G.K.; Keast, R.S.; Morel, D.; Lin, J.; Pika, J.; Han, Q.; Lee, C.H.; Smith, A.B.; Breslin, P.A. Phytochemistry: Ibuprofen-like activity in extra-virgin olive oil. *Nature* **2005**, *437*, 45–46. [[CrossRef](#)] [[PubMed](#)]
362. Angeloni, C.; Malaguti, M.; Barbalace, M.C.; Hrelia, S. Bioactivity of olive oil phenols in neuroprotection. *Int. J. Mol. Sci.* **2017**, *18*, 2230. [[CrossRef](#)] [[PubMed](#)]
363. Casamenti, F.; Stefani, M. Olive polyphenols: New promising agents to combat aging-associated neurodegeneration. *Expert. Rev. Neurother.* **2017**, *17*, 345–358. [[CrossRef](#)] [[PubMed](#)]
364. Omar, S.H.; Scott, C.J.; Hamlin, A.S.; Obied, H.K. Olive biophenols reduces Alzheimer's pathology in SH-SY5Y cells and appsw mice. *Int. J. Mol. Sci.* **2018**, *20*, 125. [[CrossRef](#)]
365. Calahorra, J.; Shenk, J.; Wielenga, V.H.; Verweij, V.; Geenen, B.; Dederen, P.J.; Peinado, M.A.; Siles, E.; Wiesmann, M.; Kiliaan, A.J. Hydroxytyrosol, the major phenolic compound of olive oil, as an acute therapeutic strategy after ischemic stroke. *Nutrients* **2019**, *11*, 2430. [[CrossRef](#)]
366. Khalatbary, A.R. Olive oil phenols and neuroprotection. *Nutr. Neurosci.* **2013**, *16*, 243–249. [[CrossRef](#)]
367. Marquez-Martin, A.; de La, P.R.; Fernandez-Arche, A.; Ruiz-Gutierrez, V.; Yaqoob, P. Modulation of cytokine secretion by pentacyclic triterpenes from olive pomace oil in human mononuclear cells. *Cytokine* **2006**, *36*, 211–217. [[CrossRef](#)] [[PubMed](#)]
368. Hornedo-Ortega, R.; Cerezo, A.B.; De Pablos, R.M.; Krisa, S.; Richard, T.; García-Parrilla, M.C.; Troncoso, A.M. Phenolic compounds characteristic of the mediterranean diet in mitigating microglia-mediated neuroinflammation. *Front. Cell Neurosci.* **2018**, *12*, 373. [[CrossRef](#)]
369. Bertelli, M.; Kiani, A.K.; Paolacci, S.; Manara, E.; Kurti, D.; Dhuli, K.; Bushati, V.; Miertus, J.; Pangallo, D.; Baglivo, M.; et al. Hydroxytyrosol: A natural compound with promising pharmacological activities. *J. Biotechnol.* **2020**, *309*, 29–33. [[CrossRef](#)]
370. Li, W.; Yin, N.; Tao, W.; Wang, Q.; Fan, H.; Wang, Z. Berberine suppresses IL-33-induced inflammatory responses in mast cells by inactivating NF-kappaB and p38 signaling. *Int. Immunopharmacol.* **2019**, *66*, 82–90. [[CrossRef](#)]
371. Fu, S.; Ni, S.; Wang, D.; Fu, M.; Hong, T. Berberine suppresses mast cell-mediated allergic responses via regulating FcγεRI-mediated and MAPK signaling. *Int. Immunopharmacol.* **2019**, *71*, 1–6. [[CrossRef](#)]
372. Zhu, J.; Cao, D.; Guo, C.; Liu, M.; Tao, Y.; Zhou, J.; Wang, F.; Zhao, Y.; Wei, J.; Zhang, Y.; et al. Berberine facilitates angiogenesis against ischemic stroke through modulating microglial polarization via AMPK signaling. *Cell Mol. Neurobiol.* **2019**, *39*, 751–768. [[CrossRef](#)] [[PubMed](#)]
373. Sengenc, E.; Kiykim, E.; Saltik, S. Vitamin D levels in children and adolescents with autism. *J. Int. Med. Res.* **2020**, *48*, 300060520934638. [[CrossRef](#)] [[PubMed](#)]
374. Petruzzelli, M.G.; Marzulli, L.; Margari, F.; De Giacomo, A.; Gabellone, A.; Giannico, O.V.; Margari, L. Vitamin D Deficiency in Autism Spectrum Disorder: A Cross-Sectional Study. *Dis. Markers* **2020**, *2020*, 9292560. [[CrossRef](#)] [[PubMed](#)]
375. Wang, Z.; Ding, R.; Wang, J. The association between vitamin D status and Autism Spectrum Disorder (ASD): A systematic review and meta-analysis. *Nutrients* **2020**, *13*, 86. [[CrossRef](#)] [[PubMed](#)]
376. Theoharides, T.C. Vitamin D and atopy. *Clin. Ther.* **2017**, *39*, 880–883. [[CrossRef](#)]
377. Chen, D.; Jia, T.; Zhang, Y.; Cao, M.; Loth, E.; Lo, C.Z.; Cheng, W.; Liu, Z.; Gong, W.; Sahakian, B.J.; et al. Neural Biomarkers Distinguish Severe from Mild Autism Spectrum Disorder Among High-Functioning Individuals. *Front Hum Neurosci.* **2021**, *15*, 657857. [[CrossRef](#)]