Serotoninergic System in Brain Disorders

Subjects: Pathology
Contributor: Denis Sarrouilhe

Serotonin (5-hydroxytryptamine, 5-HT) is a biogenic monoamine acting as a neurotransmitter in the central nervous system (CNS), local mediator in the gut, a mitogen factor, and vasoactive agent in the blood. It has been linked to a variety of CNS functions and is implicated in many CNS and psychiatric disorders. The high comorbidity between some neuropathies can be partially understood by the fact that these diseases share a common etiology involving the serotoninergic system. The developing CNS of fetus and newborn is particularly susceptible to environmental pollutants, and perinatal exposure could result in the later development of brain disorders.

Keywords: brain ; glioblastoma ; neurobehavioral disorders ; neurodegenerative disorders ; neurodevelopmental disorders ; pesticides ; pollutants ; serotonin

1. Introduction

In the CNS, serotonin is a morphogenic agent and a neurotrophic factor directing brain development during embryogenesis [1]. However, in mice and humans, before the formation of the dorsal raphe, the placenta is the source of serotonin for the early forebrain development [2]. In humans, the two first trimesters of development include cortical neurogenesis, migration, and initial axon targeting [3]. A recent study reveals that ex vivo activation of the 5-HT2A receptor in the fetal human neocortex promotes basal progenitor proliferation, cells that are linked to mammalian neocortex evolutionary expansion [4]. In mice, forebrain disruption of serotonin signaling affects axon guidance leading to abnormal thalamocortical axon trajectories [5]. Moreover, in the first postnatal week of the rodent, the serotoninergic system has a transient influence on the development of the barrel fields in layer IV of the somatosensory cortex [6]. During the last decades, the serotoninergic system emerged as a target of an increasing number of environmental pollutants, which could therefore be the source of a silent pandemic of neurodevelopmental toxicity.

2. Neurodevelopmental Disorders

The etiology of autism spectrum disorders (ASD) is believed to involve genetic, epigenetic, and environmental components [7]. In patients with ASD, an increased whole-blood serotonin level and dysfunction of the brain serotoninergic system have been described even if a clear link cannot be established between the two phenomena [8]. A hyperserotonemia is also found among some parents, brothers, and sisters of ASD children, suggesting the involvement of genetic susceptibility factors related to the serotoninergic system in ASD [9][10]. At the brain level, studies using medical imaging showed a difference in serotonin synthesis capacities, focal and asymmetrical serotonin synthesis abnormalities, and decreases in serotonin transport and binding to its receptors in ASD children compared to control children [11][12]. It is interesting to note that serotonin levels have an influence on the development and size of the barrel fields and that alterations in the organization of cortical columns have been detected in ASD [6][13]. Several studies point to the importance of serotonin for social function, cognitive flexibility, stereotypic behavior and sensory development, modulation of the processing of facial expressions of emotion, sleep-wake rhythm, and locomotion, phenomena that significantly differ in ASD patients compared with healthy control individuals [14][15][16]. Moreover, the CHARGE study showed that in boys, prenatal exposure to selective serotonin reuptake inhibitors (SSRI) such as fluoxetine, especially during the first trimesters, may be associated with an increased risk of ASD [17]. There is evidence suggesting that a number of environmental pollutants (BPA, pesticides, traffic-related air pollution, phthalates, …) contribute to ASD pathogenesis [18]. The CHARGE study reports an increased risk of ASD diagnosis among children whose mothers lived during pregnancy near fields where pesticides, particularly organophosphates, were applied [19]. A positive association was recently corroborated in the SEED study between air pollution exposure during the late prenatal and early postnatal periods and ASD [20]. Moreover, there is increasing concern that BPA exposure may influence human brain development and contributes to the increasing prevalence of ASD. For the first time, a study of 46 children with ASD and 52 controls found a direct association between children with ASD and BPA exposure and demonstrated that children with ASD do not metabolize BPA correctly. The metabolomic analyses showed a correlation between ASD and essential amino acid

metabolism pathways such as tryptophan, the serotonin precursor [21]. The aryl hydrocarbon receptor (AhR) could represent an additional level of interaction between BPA and the serotoninergic system. Indeed, BPA and some tryptophan catabolites (TRYCATs) are AhR ligands, and some of them are produced by the commensal microbiome whose involvement has been proposed in the development of ASD [22][23]. Altogether, these results suggest that the link between BPA and ASD could be a defect of in utero or perinatal serotoninergic system development or function [24].

Attention deficit hyperactivity disorders (ADHD) etiology is multifaceted, with many risk factors, including prenatal and perinatal expositions to environmental toxins, even at exposure levels considered safe for adults. Organophosphate pesticides, PCBs, lead, BPA, phthalates, and air pollution exposition have been associated with an increased risk of ADHD [25][26][27][28][29][30]. These agents may have a neurotoxic effect on the neural systems involved in ADHD [31], in particular the serotoninergic system. In rat and mouse models, fetal and prenatal BPA exposure was suggested to perturb the serotoninergic system [32][33][34], which is suspected to be involved in ADHD etiology [35]. A complex gene-environmental toxins interplay could amplify ADHD risk early on in life through epigenetic mechanisms [36]. Genetic studies identified candidate ADHD risk genes [37] such as those associated with the serotoninergic system (SLC6A4, coding for the selective serotonin transporter (SERT); HTR1B, HTR2A, coding for the 1B and 2A serotonin receptors; DDC, coding for dopamine decarboxylase; TPH2 coding for tryptophan hydroxylase 2, the neuron-specific isoform). Serotonin deficits have been proposed to be involved in the etiology of the hyperactive and impulsive component of ADHD. Interestingly, oral administration of the precursor of serotonin, tryptophan, allowed significant improvement of ADHD symptoms [38]. A recent case-control study made on 216 students and strictly matching age, sex, height, weight and class, associated ADHD with low blood levels of serotonin. Therefore, the lack of impulse control and the aggressiveness found in ADHD may be partially related to lower blood levels of serotonin [39].

Pollutant exposure during pregnancy or after birth may be at the origin of epilepsy [40]. The link underlying this association is not understood but might be mediated by serotonin levels since its increase appears to be protective against seizures and sudden unexpected death in epilepsy (SUDEP) [41]. Similarly, animal models suggest that serotonin depletion is a risk factor for epilepsy [42]. This situation is in line with studies showing that seizures and epilepsy may reduce serotonin levels and increase the risk of both seizures and SUDEP [43][44]. Therefore, any environmental exposure leading to a decrease in serotonin is susceptible to lead to an increased risk of epilepsy. This link between serotonin levels and epilepsy occurrence is illustrated by the fact that mediators of serotonin function are also involved in epilepsy. For instance, patients with temporal lobe epilepsy (TLE) exhibit decreased binding to 5-HT1A receptors within several parts of the brain [41]. Studies in epilepsy patients have also shown that seizure-induced decrease in expression of SERT contributes to reduced serotonin reuptake [45][46]. SERT binding is also reduced within the neocortex of post-mortem samples from TLE patients [47]. Moreover, seizures may influence levels of serotonin metabolites such as 5-HIAA, which is decreased in the cerebrospinal fluid (CSF) of adults with progressive myoclonic epilepsy [48][49]. Pediatric epilepsy patients also exhibit decreased concentrations of tryptophan within blood serum and CSF [50][51]. Pollution leads to neuroinflammation, which may play a role in epilepsy. In this situation, leukocytes and inflammatory mediators seem to contribute to a reduction in seizure threshold [52]. Even if their significance is unknown, immune cells from patients with TLE with hippocampal sclerosis exhibit high expression of 5-HT1A, 5-HT1B, 5-HT2A, and 5-HT4 receptors [52]. Platelets are also probably involved in this process by secreting proinflammatory mediators during neuroinflammation and traumatic brain injury (TBI). These factors increase the permeability of the BBB, which may create a predisposition to epileptic seizures, as observed in a mouse model. In this model, it is interesting to note that if platelets contribute to increased BBB permeability and are present in the CNS parenchyma during epileptic seizures, they also secrete serotonin [53]. Apparently, the presence of platelets in the CNS parenchyma is sufficient to induce severe seizures, as shown by intracranial injections of platelets that mimic TBI-associated bleeding [53]. Therefore, the role of serotonin might be different in the neuroinflammation context by favoring the risk of epilepsy.

3. Neurodegenerative Disorders

Brain neurodegenerative disorders (Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis, Friedreich’s ataxia, Huntington’s disease, …) constitute a broad corpus of diseases [54]. All of them share neuron degeneration as a common characteristic leading to overlapping clinical features such as cognitive impairment, movement disorders (called ataxias), sleep disorders, and neuronal pathway alterations (protein quality control, autophagy–lysosome pathway, mitochondria homeostasis, protein seeding, propagation of stress granules, and synaptic toxicity and network dysfunction) [55]. However, the prevalence of each of them varies greatly and affects people in an age-related manner. Rare neurodegenerative disorders (for example, amyotrophic lateral sclerosis, Friedreich’s ataxia, Huntington’s disease) mostly affect young people, whereas PD and AD affect older people and are more prevalent in countries with high life expectancy. Such epidemiological differences seem to be the consequence of genetic causes. Indeed, genetic involvement is clearly established in cases of rare neurodegenerative disorders. If genetic involvement cannot be

excluded for AD and PD, especially for younger cases, these pathologies are clearly associated with age in the general population and thus potentially with environmental exposure [56]. Therefore, due to their high prevalence in the human population and their increased risk with age [57], we will focus on the two most prevalent neurodegenerative diseases, PD and AD.

PD is a progressive neurodegenerative disorder characterized by selective degeneration of dopaminergic neurons in the substantia nigra, leading to a reduced level of dopamine in the cortex. It remains unclear whether dopaminergic neuronal death results from events triggered during development into adulthood or represents a cumulative effect throughout life. Although advanced age is the only unequivocally accepted risk factor, it has been postulated that exposure to environmental neurotoxins combined with aging could increase the risk of developing PD. Among those neurotoxins are pesticides (rotenone, paraquat, maneb, ziram). In rats, motor and depressive behaviors associated with serotonin and norepinephrine alterations induced by the administration of rotenone were observed [58]. As a major comorbidity of PD, depression is associated with the loss of serotoninergic neurons in neuronal cultures of the midbrain. The depolymerization of microtubules induced by rotenone or colchicine caused an accumulation of vesicles in the soma and killed the serotoninergic neurons by a mechanism dependent on the metabolism of serotonin in the cytosol [59]. Finally, it has been recently shown that the first signs of PD can appear in the gastrointestinal (GI) tract and in the olfactory system, preceding the onset of motor disturbances by several years. A study showed the presence of specific deficits in olfactory function associated with a concomitant decrease in tyrosine hydroxylase-positive neurons and an increase in the turnover of serotonin in the olfactory bulb. These results suggest that exposure to rotenone induces GI and olfactory dysfunction involving immunological and neurotransmitter alterations, similar to the early signs of PD. This provides further evidence for the involvement of the gut-brain axis in PD [60]. Paraquat, a widely used herbicide in the world, leads to the apoptosis of dopaminergic cells [61]. In addition, paraquat, in combination with other pesticides (maneb and ziram), increased synergistically three times the risk of developing PD [62]. One study hypothesized that exposure to paraquat and maneb during critical periods of development could permanently alter the nigrostriatal dopamine system. These results indicate that exposure to the mixture of the two pesticides during the postnatal period may produce permanent and progressive damage to the nigrostriatal dopamine system [63]. In addition, it has been shown that paraquat triggers processes characteristic of the early stages of degeneration of dopaminergic neurons and activates compensatory mechanisms involving dopaminergic, noradrenergic, serotoninergic, and GABAergic transmissions [64]. Biochemical analysis showed that paraquat and maneb reduce the tissue content of striatal dopamine alongside changes in the activity of subthalamic nucleus neurons without changing the content of norepinephrine and serotonin in the cortex [65]. Like other environmental neurotoxicants, ziram can enter the CNS from the nasal mucosa via the olfactory nerves. This is consistent with the evidence that exposure to dimethyldithiocarbamate (NaDMDC) increases the risk of PD and points to the possibility that the olfactory system may be a major pathway for entry of NaDMDC into the CNS [66].

AD has been reported to be the consequence of various risk factors such as genetic predisposition, obesity, smoking, diabetes, and exposure during life to environmental agents [67][68]. If genetic predisposition is considered to account for most cases (70%) [67][68], the part due to pollutant exposure is probably underestimated. Indeed, toxic metals (aluminum, copper, …) [69][70][71][72][73][74], pesticides (organochlorine and organophosphate insecticides: β-hexachlorocyclohexane, dieldrin, etc.) [75][76][77][78][79][80], industrial pollutants (flame retardants, BPA, phthalates, …) [81][82][83], airborne particles (PM 2.5 and PM 10) [84][85][86][87][88][89] and O 3 [88][89] have been hypothesized to induce or aggravate AD. Despite their chemical and physical variety, these pollutants seem to act through a common process, neuroinflammation, due to microglia activation, which is known to play an essential role in neurodegenerative diseases such as AD and PD [85][86][90][91][92]. Activated microglia are known to release proinflammatory factors, such as TNFα and IL-1β [93][94], which are found to be increased in the CSF of patients with AD [95][96][97]. Neuritic plaques composed of Aβ and neurofibrillary tangles are, indeed, surrounded by astrocytes and microglia with reactive characteristics [98]. Interestingly, proinflammatory factors have been observed in biological samples (blood, urine, and necropsy tissue) of children and adults from polluted areas [92][99][100][101] and were related to amyloid processing (tau hyperphosphorylation, Aβ immunoreactivity, and plaques) and inflammation response in the human brain [99][100][101][102]. Similar observations linking brain damage (white matter lesions, damaged BBB, degenerating neurons) and neuroinflammation were made in dogs from highly polluted urban areas compared to dogs living in rural areas [103][104][105]. All these observations have been confirmed by experimental data obtained from rodent models. Indeed, such data demonstrate that PM (PM 0.1 , PM 2.5) exposures elicit increased brain inflammation, measured by IL-1β and TNFα [106][107][108][109]. Such a phenomenon is accompanied, for longer exposures (30–39 weeks), by brain damage (loss of dendritic spine density in the CA1 region of the hippocampus) and buildup of Aβ plaques, which correlates with impaired cognitive outcomes [110][111]. Other kinds of exposures, as diesel exhaust particles or nickel nanoparticles, also lead to increased inflammatory cytokines (TNFα, IL-1β) and increased levels of Aβ42 in multiple brain regions of rats [112][113] and mice [114], suggesting that the effect on Aβ buildup in the brain may be, in part, due to the concentration of particulates exposed, rather than its chemical constituents. Globally, all these findings demonstrate the association between chronic exposure to PM and inflammation and the development of AD-like

neuropathology. Interestingly, the use of transgenic mice also confirmed that PM exposure effects on AD pathogenesis can be increased with susceptible genotypes, as seen in epidemiological studies [115][116]. A possible link between neuroinflammation and AD could be mediated by the attachment of complement proteins, such as complement C3, which helps microglia in the clearing of the plaques and is up-regulated in AD, contributing to the synapse loss that leads to cognitive decline [117][118]. It was demonstrated that knocking out the gene of this molecule in mice models of AD improved the animals' performance in both learning and memory tests, despite them having more plaques in their brains and fewer activated microglia [119]. Increased proinflammatory cytokines in AD, such as IL-1β and TNFα, impact the serotoninergic system by increasing the uptake rate of serotonin [120] through SERT [121]. Therefore, such an effect could lead to decreased serotonin levels, which might be related to depression that is currently observed in AD patients. Such a hypothesis is supported by studies reporting that accumulation of Aβ oligomers and toxins present in AD patients leads to depressive episodes in mice through microglial activation, alterations in the TNFα signaling pathway, and reduced presence of serotonin in the brain [122]. Interestingly, it has been shown that treatments with SSRIs reduce the number of cytokines in the circulation [123][124]. Moreover, the following increased levels of serotonin resulted in lower Aβ production, supporting the idea that serotonin-induced pathways influence Aβ deposits in a negative way [125]. Such an effect is probably linked with the fact that serotonin can prevent the activation of microglial cells that are induced by Aβ [122]. Therefore, the modulation of the serotoninergic system may represent a therapeutic target for AD treatment, as suggested by recent clinical data [126].

To summarize, it does not seem that pollutant exposure induces AD by directly impairing the serotoninergic system. According to our current knowledge, pollutants first activate neuroinflammation in the brain, which, in turn, leads to brain damage. Among such damage, the serotoninergic dorsal raphe nucleus can be one of the first brain locations to be affected by tau protein abnormalities [127] even if the degeneration of the serotoninergic system can be observed in other brain regions (cortical, striatal, thalamic, and limbic regions) of patients with cognitive impairments compared to cognitively normal controls [128].

4. Neurobehavioral Disorders

Mood and emotional disturbances are common complications observed in post-stroke patients [129] and may manifest when the lesions damage the serotoninergic neuronal system. Accordingly, SSRIs are the first-line medication choice to treat depressive symptoms in stroke patients and generally improve mood symptoms [130]. Emerging data suggest a role of serotonin in the recovery of neurological dysfunction in stroke patients, but the efficacy of SSRIs to improve emotional disturbances and/or neurological dysfunction may depend on SERT gene polymorphisms [131].

Multiple sclerosis (MS) is a progressive neurological disorder in which environmental and genetic etiologies were suspected. In this disease, the immune system attacks and destructs the myelin protective sheath that covers nerve fibers resulting in CNS dysfunction. Both synthesis and metabolism of serotonin are disrupted in the brain of patients with MS. The level of tryptophan is reduced in the plasma and the CSF of patients, changes that might lead to impaired synthesis of brain serotonin [132][133]. On the other hand, a low level of 5-HIAA was found in CSF of patients with MS [134]. In a proof-of-concept study, the SSRI fluoxetine has a neuroprotective effect by reducing the formation of new lesions in non-depressed MS patients [135]. Nevertheless, depression is a common comorbidity observed in MS, and dysregulation of the serotoninergic system is observed in both diseases. Thus, reregulation of the serotoninergic system with SSRIs was also effective in MDD treatment in MS patients [136][137].

Toxic encephalopathies are caused by acute or chronic exposures to various substances and pollutants that can act as neurotoxicants (see also paragraph 2 for the effects of pollutants on the serotoninergic system). They are characterized by several symptoms, including an altered mental status, seizures, and depressive mood. Toxic encephalopathy was described in patients following co-administration of the dye methylene blue to enable pre-operative visualization of parathyroid glands and SSRI. This dye being a potent MAO-A inhibitor, severe serotonin toxicity (or serotonin syndrome) was suggested [138]. Most cases of serotonin toxicity involve an overdose of serotonin-elevating drugs, monoamine-oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors (SNRIs), and SSRIs.

Major depressive disorders (MDD) are psychiatric illnesses with an etiology determined by a complex set of influences (genetic, social, and environmental). Despite advances in the understanding of the etiology and pathophysiology of MDD [139], currently, no established mechanism can explain all facets of the disease. Among the neurophysiological theories of this disease, the monoamine hypothesis proposes a deficiency of central monoamine systems, including the serotoninergic [140]. Many antidepressant drugs act by inhibiting the reuptake of one or more monoamine neurotransmitters or by an increase in neurotransmitters release and thus improve the neurotransmission system altered in MDD. For example, SSRIs, some of the most commonly prescribed drugs worldwide, inhibit serotonin uptake through the blockage of neuronal and astrocytic SERT, and the subsequent enhancement of synaptic serotonin levels is known to

act on 5-HT receptors that mediate antidepressant response. Moreover, reduced serotoninergic neurotransmission is a hypothesis to explain the etiology of suicide [141]. Two other hypotheses, the neurotrophic and neurogenic hypotheses, have been proposed to explain the role of serotonin in the pathophysiology of depression. These hypotheses are based on the fact that 5-HT receptors and 5-HT signaling are involved in regulating the levels of both neurotrophic factors (i.e., BDNF, VEGF, FGF2, IGF1) and adult neurogenesis in the subgranular zone of the dentale gyrus in the hippocampus [142]. In a previous review, we reported that many environmental chemical pollutants had been related to the etiology of MDD [40]. Several epidemiological studies suggest that exposure to BPA [143] phthalates [144][145], heavy metals [143], PAH [145], pesticides [143], and airborne pollutants [146] contribute to an increased prevalence of MDD. Moreover, in mice, early life exposure to BPA dose, representative of human exposure levels, induces depressive-like behavior specific to F1 generation adult males, associated with a reduction in whole hippocampal serotonin levels [147]. Interestingly, hippocampal and frontal cortex serotonin levels were reduced in a stress-sensitive rat model of depression following chronic O 3 exposure [148].

References

1. Azmitia, E.C. Modern views on an ancient chemical: Serotonin effects on cell proliferation, maturation, and apoptosis. B rain Res. Bull. 2001, 56, 413–424.
2. Bonnin, A.; Goeden, N.; Chen, K.; Wilson, M.L.; King, J.; Shih, J.C.; Blakely, R.D.; Deneris, E.S.; Levitt, P. A transient pl acental source of serotonin for the fetal forebrain. Nature 2011, 472, 347–350.
3. Bonnin, A.; Levitt, P. Fetal, maternal, and placental sources of serotonin and new implications for developmental progra mming of the brain. Neuroscience 2011, 197, 1–7.
4. Xing, L.; Kalebic, N.; Namba, T.; Vaid, S.; Wimberger, P.; Huttner, V.B. Serotonin receptor 2A activation promotes evolut ionarily relevant basal progenitor proliferation in the developing neocortex. Neuron 2020, 108, 1–17.
5. Bonnin, A.; Torii, M.; Wang, L.; Rakic, P.; Levitt, P. Serotonin modulates the response of embryonic thalamocortical axo ns to netrin-1. Nat. Neurosci. 2007, 10, 588–597.
6. Blue, M.E.; Johnston, M.V.; Moloney, C.B.; Hohmann, C.F. Serotonin dysfunction in autism. In Autism; Zimmerman, A. W., Ed.; Humana Press: Totowa, NJ, USA, 2008; pp. 111–132.
7. Grandjean, P.; Landrigan, P.J. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 2014, 13, 330–338.
8. Janusonis, S.; Anderson, G.M.; Shifrovich, I.; Rakic, P. Ontogeny of brain and blood serotonin levels in 5-HT receptor k nockout mice: Potential relevance to the neurobiology of autism. J. Neurochem. 2006, 99, 1019–1031.
9. Leboyer, M.; Philippe, A.; Bouvard, M.; Guilloud-Bataille, M.; Bondoux, D.; Tabuteau, F.; Feingold, J.; Moure Si Meoni, M.C.; Launay, J.M. Whole blood serotonin and plasma beta-endorphin in autistic probands and their first-degree relativ es. Biol. Psychiatry 1999, 45, 158–163.
10. Pagan, C.; Delorme, R.; Callebert, J.; Goubran-Botros, H.; Ansellem, F.; Drouot, X.; Boudebesse, C.; Le Dudal, K.; Ngo -Nguyen, N.; Laouamri, H.; et al. The serotonin-N-acetylserotonin-melatonin pathway as a biomarker for autism spectru m disorders. Transl. Psychiatry 2014, 4, e479.
11. Chandana, S.R.; Behen, M.E.; Juhász, C.; Muzik, O.; Rothermel, R.D.; Mangner, T.J.; Chakraborty, P.K.; Chugani, H.T.; Chugani, D.C. Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis i n autism. Int. J. Dev. Neurosci. 2005, 23, 171–182.
12. Chugani, D.C. Application of PET and SPECT to the study of autism spectrum disorders. In PET and SPECT in Psychi atry; Dierckx, R.A.J.O., Otte, A., de Vries, E.F.J., van Waarde, A., den Boer, J.A., Eds.; Springer: Berlin/Heidelberg, Ger many, 2014; pp. 691–707.
13. Casanova, M.F.; van Kooten, I.A.; Switala, A.E.; van Engeland, H.; Heinsen, H.; Steinbusch, H.W.; Hof, P.R.; Trippe, J.; Stone, J.; Schmitz, C. Minicolumnar abnormalities in autism. Acta Neuropathol. 2006, 112, 287–303.
14. Nomura, Y.; Nagao, Y.; Kimura, K.; Hachimori, K.; Segawa, M. Epilepsy in autism: A pathophysiological consideration. Brain Dev. 2010, 32, 799–804.
15. Daly, E.M.; Deeley, Q.; Ecker, C.; Craig, M.; Hallahan, B.; Murphy, C.; Johnston, P.; Spain, D.; Gillan, N.; Brammer, M.; et al. Serotonin and the neural processing of facial emotions in adults with autism: An fMRI study using acute tryptopha n depletion. Arch. Gen. Psychiatry 2012, 69, 1003–1013.
16. Muller, C.L.; Anacker, A.M.J.; Veenstra-VanderWeele, J. The serotonin system in autism spectrum disorder: From biom arker to animal models. Neuroscience 2016, 321, 24–41.

17. Harrington, R.A.; Lee, L.C.; Crum, R.M.; Zimmerman, A.W.; Hertz-Picciotto, I. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. Pediatrics 2014, 133, e1241–e1248.

18. Ye, B.S.; Leung, A.O.W.; Wong, M.H. The association of environmental toxicants and autism spectrum disorders in children. Environ. Pollut. 2017, 227, 234–242.

19. Shelton, J.F.; Geraghty, E.M.; Tancredi, D.J.; Delwiche, L.D.; Schmidt, R.J.; Ritz, B.; Hansen, R.L.; Hertz-Picciotto, I. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: The CHARGE study. Environ. Health Perspect. 2014, 122, 10.

20. McGuinn, L.A.; Windham, G.C.; Kalkbrenner, A.E.; Bradley, C.; Di, Q.; Croen, L.A.; Fallin, M.D.; Hoffman, K.; Ladd-Acosta, C.; Schwartz, J.; et al. Early life exposure to air pollution and autism spectrum disorder: Findings from a multisite case-control study. Epidemiology 2020, 31, 103–114.

21. Stein, T.P.; Schluter, M.D.; Steer, R.A.; Guo, L.; Ming, X. Bisphenol A exposure in children with autism spectrum disorders. Autism Res. 2015, 8, 272–283.

22. Hsiao, E.Y.; McBride, S.W.; Hsien, S.; Sharon, G.; Hyde, E.R.; McCue, T.; Codelli, J.A.; Chow, J.; Reisman, S.E.; Petrosino, J.F.; et al. The micobiota modulates gut physiology and behavioral abnormalities associated with autism. Cell 2013, 155, 1451–1463.

23. Noakes, R. The aryl hydrocarbon receptor: A review of its role in the physiology and pathology of the integument and its relationship to the tryptophan metabolism. Int. J. Tryptophan Res. 2015, 8, 7–18.

24. Sarrouilhe, D.; Dejean, C. Autism spectrum disorders and bisphenol A: Is serotonin the lacking link in the chain? L'Encéphale 2017, 43, 402–404.

25. Marks, A.R.; Harley, K.; Bradman, A.; Kogut, K.; Barr, D.B.; Johnson, C.; Eskenazi, B. Organophosphate pesticide exposure and attention in young Mexican-American children: The CHAMACOS study. Environ. Health Perspect. 2010, 118, 1768–1774.

26. Sagiv, S.K.; Thurston, S.W.; Bellinger, D.C.; Tolbert, P.E.; Altshul, L.M.; Korrick, S.A. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. Am. J. Epidemiol. 2010, 171, 593–601.

27. Nigg, J.; Nikolas, M.; Mark Knowttnerus, G.; Kavanagh, K.; Friderici, K. Confirmation and extension of association of blood lead with attention-deficit/hyperactivity disorder (ADHD) and ADHD symptom domains at population typical exposure levels. J. Child Psychol. Psych. 2010, 51, 58–65.

28. Engel, S.M.; Villanger, G.D.; Nethery, R.C.; Thomsen, C.; Sakhi, A.K.; Drover, S.S.M.; Hoppin, J.A.; Zeiner, P.; Knudsen, G.P.; Reichborn-Kjennerud, T.; et al. Prenatal Phthalates, Maternal Thyroid Function, and Risk of Attention-Deficit Hyperactivity Disorder in the Norwegian Mother and Child Cohort. Environ. Health Perspect. 2018, 126, 5.

29. Braun, J.M.; Yolton, K.; Dietrich, K.N.; Hornung, R.; Ye, X.; Calafat, A.M.; Lanphear, B.P. Prenatal bisphenol A exposure and early childhood behavior. Environ. Health Perspect. 2009, 117, 1945–1952.

30. Yorifuji, T.; Kashima, S.; Diez, M.H.; Kado, Y.; Sanada, S.; Doi, H. Prenatal exposure to outdoor air pollution and child behavioral problems at school age in Japan. Environ. Int. 2017, 99, 192–198.

31. Nigg, J.T. ADHD, lead exposure and prevention: How much lead or how much evidence is needed? Expert Rev. Neurother. 2008, 8, 519–521.

32. Honma, T.; Miyagawa, M.; Suda, M.; Wang, R.S.; Kobayashi, K.; Sekiguchi, S. Effects of perinatal exposure to bisphenol A on brain neurotransmitters in female rat offspring. Ind. Health 2006, 44, 510–524.

33. Matsuda, S.; Saika, S.; Amano, K.; Shimizu, E.; Sajiki, J. Changes in brain monoamine levels in neonatal rats exposed to bisphenol A at low doses. Chemosphere 2010, 78, 894–906.

34. Nakamura, K.; Itoh, K.; Yoshimoto, K.; Sugimoto, T.; Fushiki, S. Prenatal and lactational exposure to low-doses of bisphenol A alters brain monoamine concentration in adult mice. Neurosci. Lett. 2010, 484, 66–70.

35. Rochester, J.R.; Bolden, A.L.; Kwiatkowski, C.F. Prenatal exposure to bisphenol A and hyperactivity in children: A systematic review and meta-analysis. Environ. Int. 2018, 114, 343–356.

36. Thapar, A.; Cooper, M.; Eyre, O.; Langley, K. What have we learnt about the causes of ADHD? J. Child. Psychol. Psychiatry 2013, 54, 3–16.

37. Banaschewski, T.; Becker, K.; Scherag, S.; Franke, B.; Coghill, D. Molecular genetics of attention-deficit/hyperactivity disorder: An overview. Eur. Child. Adolesc. Psychiatry 2010, 19, 237–257.

38. Banerjee, E.; Nandagopal, K. Does serotonin deficit mediate susceptibility to ADHD? Neurochem. Int. 2015, 82, 52–68.

39. Wang, L.J.; Yu, Y.H.; Fu, M.L.; Yeh, W.T.; Hsu, J.L.; Yang, Y.H.; Chen, W.J.; Chiang, B.L.; Pan, W.H. Attention deficit–hyperactivity disorder is associated with allergic symptoms and low levels of hemoglobin and serotonin. Sci. Rep. 2018, 8,

10229.

40. Mesnil, M.; Defamie, N.; Naus, C.; Sarrouilhe, D. Brain disorders and chemical pollutants: A gap junction link? Biomolec ules 2021, 11, 51.
41. Petrucci, A.N.; Joyal, K.G.; Purnell, B.S.; Buchanan, G.F. Serotonin and sudden unexpected death in epilepsy. Exp. Ne urol. 2020, 325, 113145.
42. Maia, G.H.; Brazete, C.S.; Soares, J.I.; Luz, L.L.; Lukoyanov, N.V. Serotonin depletion increases seizure susceptibility a nd worsens neuropathological outcomes in kainate model of epilepsy. Brain Res. Bull. 2017, 134, 109–120.
43. Bagdy, G.; Kecskemeti, V.; Riba, P.; Jakus, R. Serotonin and epilepsy. J. Neurochem. 2007, 100, 857–873.
44. Richerson, G.B.; Buchanan, G.F. The serotonin axis: Shared mechanisms in seizures, depression, and SUDEP. Epilep sia 2011, 52, 28–38.
45. Schenkel, L.C.; Bragatti, J.A.; Torres, C.M.; Martin, K.C.; Gus-Manfro, G.; Leistner-Segal, S.; Bianchin, M.M. Serotonin transporter gene (5HTT) polymorphisms and temporal lobe epilepsy. Epilepsy Res. 2011, 95, 152–157.
46. Esmail, E.H.; Labib, D.M.; Rabie, W.A. Association of serotonin transporter gene (5HTT) polymorphism and juvenile my oclonic epilepsy: A case-control study. Acta Neurol. Belg. 2015, 115, 247–251.
47. Rocha, L.; Lorigados-Pedre, L.; Orozco-Suarez, S.; Morales-Chacon, L.; Alonso-Vanegas, M.; Garcia-Maeso, I.; Villeda -Hernández, J.; Osorio-Rico, L.; Estupiñán, B.; Quintana, C. Autoradiography reveals selective changes in serotonin bi nding in neocortex of patients with temporal lobe epilepsy. Prog. Neuropsychopharmacol. Biol. Psychiatry 2007, 31, 12 08–1218.
48. Giroud, M.; Dumas, R.; Dauvergne, M.; D'Athis, P.; Rochette, L.; Beley, A.; Bralet, J. 5-Hydroxyindoleacetic acid and ho movanillic acid in cerebrospinal fluid of children with febrile convulsions. Epilepsia 1990, 31, 178–181.
49. Pranzatelli, M.R.; Tate, E.; Huang, Y.; Haas, R.H.; Bodensteiner, J.; Ashwal, S.; Franz, D. Neuropharmacology of progre ssive myoclonus epilepsy: Response to 5-hydroxy-L-tryptophan. Epilepsia 1995, 36, 783–791.
50. Marion, J.L.; Bigot, J.C.; Goas, J.Y. Alcoholic epilepsy—Low tryptophan levels in plasma and cerebrospinal-fluid. Press e Med. 1985, 14, 681–683.
51. Ko, F.J.; Chiang, C.H.; Liu, W.J.; Chiang, W. Alteration of amino acid in plasma and cerebrospinal fluid of children with s eizure disorders. Gaoxiong Yi Xue Ke Xue Za Zhi 1993, 9, 131–142.
52. Vieira, É.L.M.; da Silva, M.C.M.; Gonçalves, A.P.; Martins, G.L.; Teixeira, A.L.; de Oliveira, A.C.P.; Reis, H.J. Serotonin and dopamine receptors profile on peripheral immune cells from patients with temporal lobe epilepsy. J. Neuroimmunol. 2021, 354, 577534.
53. Kopeikina, E.; Dukhinova, M.; Yung, A.W.Y.; Veremeyko, T.; Kuznetsova, I.S.; Lau, T.Y.B.; Levchuk, K.; Ponomarev, E. D. Platelets promote epileptic seizures by modulating brain serotonin level, enhancing neuronal electric activity, and co ntributing to neuroinflammation and oxidative stress. Prog. Neurobiol. 2020, 188, 101783.
54. Dugger, B.N.; Dickson, D.W. Pathology of Neurodegenerative Diseases. Cold Spring Harb. Perspect. Biol. 2017, 9, a02 8035.
55. Gan, L.; Cookson, M.R.; Petrucelli, L.; La Spada, A.R. Converging pathways in neurodegeneration, from genetics to me chanisms. Nat. Neurosci. 2018, 21, 1300–1309.
56. Wyss-Coray, T. Ageing, neurodegeneration and brain rejuvenation. Nature 2016, 539, 180–186.
57. Hou, Y.; Dan, X.; Babbar, M.; Wei, Y.; Hasselbalch, S.G.; Croteau, D.L.; Bohr, V.A. Ageing as a risk factor for neurodege nerative disease. Nat. Rev. Neurol. 2019, 15, 565–581.
58. Morais, L.H.; Lima, M.M.; Martynhak, B.J.; Santiago, R.; Takahashi, T.T.; Ariza, D.; Barbiero, J.K.; Andreatini, R.; Vital, M.A. Characterization of motor, depressive-like and neurochemical alterations induced by a short-term rotenone admini stration. Pharmacol. Rep. 2012, 64, 1081–1090.
59. Ren, Y.; Feng, J. Rotenone selectively kills serotonergic neurons through a microtubule-dependent mechanism. J. Neur ochem. 2007, 103, 303–311.
60. Morais, L.H.; Hara, D.B.; Bicca, M.A.; Poli, A.; Takahashi, R.N. Early signs of colonic inflammation, intestinal dysfunctio n, and olfactory impairments in the rotenone-induced mouse model of Parkinson's disease. Behav. Pharmacol. 2018, 2 9, 199–210.
61. Tanner, C.M.; Kamel, F.; Ross, G.W.; Hoppin, J.A.; Goldman, S.M.; Korell, M.; Marras, C.; Bhudhikanok, G.S.; Kasten, M.; Chade, A.R.; et al. Rotenone, paraquat, and Parkinson's disease. Environ. Health Perspect. 2011, 119, 866–872.
62. Wang, A.; Costello, S.; Cockburn, M.; Zhang, X.; Bronstein, J.; Ritz, B. Parkinson's disease risk from ambient exposure to pesticides. Eur. J. Epidemiol. 2011, 26, 547–555.

63. Thiruchelvam, M.; Richfield, E.K.; Goodman, B.M.; Baggs, R.B.; Cory-Slechta, D.A. Developmental exposure to the pesticides paraquat and maneb and the Parkinson's disease phenotype. Neurotoxicology 2002, 23, 621–633.

64. Kuter, K.; Smiałowska, M.; Wierońska, J.; Zieba, B.; Wardas, J.; Pietraszek, M.; Nowak, P.; Biedka, I.; Roczniak, W.; Konieczny, J.; et al. Toxic influence of subchronic paraquat administration on dopaminergic neurons in rats. Brain Res. 2007, 1155, 196–207.

65. Tinakoua, A.; Bouabid, S.; Faggiani, E.; De Deurwaerdère, P.; Lakhdar-Ghazal, N.; Benazzouz, A. The impact of combined administration of paraquat and maneb on motor and non-motor functions in the rat. Neuroscience 2015, 311, 118–129.

66. Mack, J.M.; Moura, T.M.; Lanznaster, D.; Bobinski, F.; Massari, C.M.; Sampaio, T.B.; Schmitz, A.E.; Souza, L.F.; Walz, R.; Tasca, C.I.; et al. Intranasal administration of sodium dimethyldithiocarbamate induces motor deficits and dopaminergic dysfunction in mice. Neurotoxicology 2018, 66, 107–120.

67. Avramopoulos, D. Genetics of Alzheimer's disease: Recent advances. Genome Med. 2009, 1, 34.

68. Ballard, C.; Gauthier, S.; Corbett, A.; Brayne, C.; Aarsland, D.; Jones, E. Alzheimer's disease. Lancet 2011, 377, 1019–1031.

69. Campbell, A. The potential role of aluminium in Alzheimer's disease. Nephrol. Dial. Transplant. 2002, 17, 17–20.

70. Crapper, D.R.; Krishnan, S.S.; Dalton, A.J. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 1973, 180, 511–513.

71. Kawahara, M.; Kato-Negishi, M. Link between aluminum and the pathogenesis of Alzheimer's disease: The integration of the aluminum and amyloid cascade hypotheses. Int. J. Alzheimer's Dis. 2011, 2011, 276393.

72. Sparks, D.L.; Schreurs, B.G. Trace amounts of copper in water induce β-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. Proc. Natl. Acad. Sci. USA 2003, 100, 11065–11069.

73. Syme, C.D.; Nadal, R.C.; Rigby, S.E.J.; Viles, J.H. Copper binding to the amyloid-β (Aβ) peptide associated with Alzheimer's disease: Folding, coordination geometry, pH dependence, stoichiometry, and affinity of Aβ-(1–28): Insights from a range of complementary spectroscopic techniques. J. Biol. Chem. 2004, 279, 18169–18177.

74. Singh, I.; Sagare, A.P.; Coma, M.; Perlmutter, D.; Gelein, R.; Bell, R.D.; Deane, R.J.; Zhong, E.; Parisi, M.; Ciszewski, J.; et al. Low levels of copper disrupt brain amyloid-β homeostasis by altering its production and clearance. Proc. Natl. Acad. Sci. USA 2013, 110, 14771–14776.

75. Baldi, I.; Lebailly, P.; Mohammed-Brahim, B.; Letenneur, L.; Dartigues, J.-F.; Brochard, P. Neurodegenerative diseases and exposure to pesticides in the elderly. Am. J. Epidemiol. 2003, 157, 409–414.

76. Chhillar, N.; Singh, N.K.; Banerjee, B.D.; Bala, K.; Sharma, D.; Mitrabasu, M. β-hexachlorocyclohexane as a risk for Alzheimer's disease: A pilot study in North Indian population. Am. J. Alzheimer's Dis. 2013, 1, 60–71.

77. Richardson, J.R.; Roy, A.; Shalat, S.L.; von Stein, R.T.; Hossain, M.M.; Buckley, B.; Gearing, M.; Levey, A.I.; German, D.C. Elevated serum pesticide levels and risk for alzheimer disease. JAMA Neurol. 2014, 71, 284–290.

78. Zaganas, I.; Kapetanaki, S.; Mastorodemos, V.; Kanavouras, K.; Colosio, C.; Wilks, M.F.; Tsatsakis, A.M. Linking pesticide exposure and dementia: What is the evidence? Toxicology 2013, 307, 3–11.

79. Hayden, K.M.; Norton, M.C.; Darcey, D.; Østbye, T.; Zandi, P.P.; Breitner, J.C.S.; Welsh-Bohmer, K.A.; Cache County Study Investigators. Occupational exposure to pesticides increases the risk of incident AD: The Cache County Study. Neurology 2010, 74, 1524–1530.

80. Singh, N.; Chhillar, N.; Banerjee, B.; Bala, K.; Basu, M.; Mustafa, M. Organochlorine pesticide levels and risk of Alzheimer's disease in north Indian population. Hum. Exp. Toxicol. 2013, 32, 24–30.

81. Al-Mousa, F.; Michelangeli, F. Some Commonly Used Brominated Flame Retardants Cause Ca2+-ATPase Inhibition, Beta-Amyloid Peptide Release and Apoptosis in SH-SY5Y Neuronal Cells. PLoS ONE 2012, 7, e33059.

82. Hajszan, T.; Leranth, C. Bisphenol A interferes with synaptic remodeling. Front. Neuroendocrinol. 2010, 31, 519–530.

83. Sun, W.; Ban, J.-B.; Zhang, N.; Zu, Y.-K.; Sun, W.-X. Perinatal exposure to di-(2-ethylhexyl)-phthalate leads to cognitive dysfunction and phospho-tau level increase in aged rats. Environ. Toxicol. 2014, 29, 596–603.

84. Yegambaram, M.; Manivannan, B.; Beach, T.G.; Halden, R.U. Role of environmental contaminants in the etiology of Alzheimer's disease: A review. Curr. Alzheimer Res. 2015, 12, 116–146.

85. Kilian, J.; Kitazawa, M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease—Evidence from epidemiological and animal studies. Biomed. J. 2018, 41, 141–162.

86. Wang, J.; Ma, T.; Ma, D.; Li, H.; Hua, L.; He, Q.; Deng, X. The Impact of Air Pollution on Neurodegenerative Diseases. Ther. Drug Monit. 2021, 43, 69–78.

87. Kioumourtzoglou, M.A.; Schwartz, J.D.; Weisskopf, M.G.; Melly, S.J.; Wang, Y.; Dominici, F.; Zanobetti, A. Long-term P M2.5 exposure and neurological hospital admissions in the northeastern United States. Environ. Health Perspect. 201 6, 124, 23–29.

88. Jung, C.R.; Lin, Y.T.; Hwang, B.F. Ozone, particulate matter, andnewly diagnosed Alzheimer's disease: A population-ba sed cohort study in Taiwan. J. Alzheimer's Dis. 2015, 44, 573–584.

89. Wu, Y.C.; Lin, Y.C.; Yu, H.L.; Chen, J.H.; Chen, T.F.; Sun, Y.; Wen, L.-L.; Yip, R.-K.; Chu, Y.-M.; Chen, Y.-C. Association between air pollutants and dementia risk in the elderly. Alzheimer's Dement. Diagn. Assess. Dis. Monit. 2015, 1, 220–2 28.

90. Correia, A.S.; Cardoso, A.; Vale, N. Highlighting Immune System and Stress in Major Depressive Disorder, Parkinson's, and Alzheimer's Diseases, with a Connection with Serotonin. Int. J. Mol. Sci. 2021, 22, 8525.

91. Heppner, F.L.; Ransohoff, R.M.; Becher, B. Immune attack: The role of inflammation in Alzheimer disease. Nat. Rev. Ne urosci. 2015, 16, 358–372.

92. Calderon-Garciduenas, L.; Kavanaugh, M.; Block, M.L.; D'Angiulli, A.; Delgado-Chavez, R.; Torres-Jardon, R.; Gonzále z-Maciel, A.; Reynoso-Robles, R.; Osnaya, N.; Villarreal-Calderon, R.; et al. Neuroinflammation, hyperphosphorilated ta u, diffuse amyloid plaques and down-regulation of the cellular prion protein in air pollution exposed children and adults. J. Alzheimer's Dis. 2012, 28, 93–107.

93. Wang, W.Y.; Tan, M.S.; Yu, J.T.; Tan, L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disea se. Ann. Transl. Med. 2015, 3, 136.

94. Heneka, M.T.; Kummer, M.P.; Stutz, A.; Delekate, A.; Schwartz, S.; Vieira-Saecker, A.; Griep, A.; Axt, D.; Remus, A.; Tz eng, T.C.; et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature 2013, 493, 674–678.

95. Smith, J.A.; Das, A.; Ray, S.K.; Banik, N.L. Role of pro-inflammatory cytokines released from microglia in neurodegener ative diseases. Brain Res. Bull. 2012, 87, 10–20.

96. Cribbs, D.H.; Berchtold, N.C.; Perreau, V.; Coleman, P.D.; Rogers, J.; Tenner, A.J.; Cotman, C.W. Extensive innate imm une gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: A mi croarray study. J. Neuroinflamm. 2012, 9, 1–18.

97. Ojala, J.; Alafuzoff, I.; Herukka, S.K.; van Groen, T.; Tanila, H.; Pirttilä, T. Expression of interleukin-18 is increased in the brains of Alzheimer's disease patients. Neurobiol. Aging 2009, 30, 198–209.

98. Serrano-Pozo, A.; Mielke, M.L.; Gómez-Isla, T.; Betensky, R.A.; Growdon, J.H.; Frosch, M.P.; Hyman, B.T. Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. Am. J. Pathol. 2011, 179, 1373–138 4.

99. Calderon-Garciduenas, L.; Reed, W.; Maronpot, R.R.; Henriquez-Roldan, C.; Delgado-Chavez, R.; Calderon-Garciduen as, A.; Dragustinovis, I.; Franco-Lira, M.; Aragón-Flores, M.; Solt, A.C.; et al. Brain inflammation and Alzheimer's-like pa thology in individuals exposed to severe air pollution. Toxicol. Pathol. 2004, 32, 650–658.

100. Calderon-Garciduenas, L.; Solt, A.C.; Henriquez-Roldan, C.; Torres-Jardon, R.; Nuse, B.; Herritt, L.; Villarreal-Calderó n, R.; Osnaya, N.; Stone, I.; García, R.; et al. Long-term air pollution exposure is associated with neuroinflammation, an altered innate immune response, disruption of the blood-brain barrier, ultrafine particulate deposition, and accumulation of amyloid β-42 and α-synuclein in children and young adults. Toxicol. Pathol. 2008, 36, 289–310.

101. Calderon-Garciduenas, L.; Mora-Tiscareno, A.; Styner, M.; Gomez-Garza, G.; Zhu, H.; Torres-Jardon, R.; Carlos, E.; So lorio-López, E.; Medina-Cortina, H.; Kavanaugh, M.; et al. White matter hyperintensities, systemic inflammation, brain g rowth, and cognitive functions in children exposed to air pollution. J. Alzheimer's Dis. 2012, 31, 183–191.

102. Calderon-Garciduenas, L.; Franco-Lira, M.; Henriquez-Roldan, C.; Osnaya, N.; Gonzalez-Maciel, A.; Reynoso-Robles, R.; Villarreal-Calderon, R.; Herritt, L.; Brooks, D.; Keefe, S.; et al. Urban air pollution: Influences on olfactory function a nd pathology in exposed children and young adults. Exp. Toxicol. Pathol. 2010, 62, 91–102.

103. Calderón-Garcidueñas, L.; Azzarelli, B.; Acuna, H.; Garcia, R.; Gambling, T.; Osnaya, N. Air pollution and brain damag e. Toxicol. Pathol. 2002, 30, 373–389.

104. Calderon-Garciduenas, L.; Maronpot, R.R.; Torres-Jardon, R.; Henriquez-Roldan, C.; Schoonhoven, R.; Acuna-Ayala, H. DNA damage in nasal and brain tissues of canines exposed to air pollutants is associated with evidence of chronic b rain inflammation and neurodegeneration. Toxicol. Pathol. 2003, 31, 524–538.

105. Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Ontiveros, E.; Gómez-Garza, G.; Barragán-Mejía, G.; Broadway, J. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. Brain Cognit. 2008, 68, 117–1 27.

106. Cheng, H.; Saffari, A.; Sioutas, C.; Forman, H.J.; Morgan, T.E.; Finch, C.E. Nanoscale particulate matter from urban traf fic rapidly induces oxidative stress and inflammation in olfactory epithelium with concomitant effects on brain. Environ. Health Perspect. 2016, 124, 1537–1546.

107. Guerra, R.; Vera-Aguilar, E.; Uribe-Ramirez, M.; Gookin, G.; Camacho, J.; Osornio-Vargas, A.R. Exposure to inhaled p articulate matter activates early markers of oxidative stress, inflammation and unfolded protein response in rat striatum. Toxicol. Lett. 2013, 222, 146–154.

108. Kleinman, M.T.; Araujo, J.; Nel, A.; Sioutas, C.; Campbell, A.; Cong, P.Q. Inhaled ultrafine particulate matter affects CN S inflammatory processes and may act via MAP kinase signaling pathways. Toxicol. Lett. 2008, 178, 127–130.

109. Campbell, A.; Oldham, M.; Becaria, A.; Bondy, S.C.; Meacher, D.; Sioutas, C. Particulate matter in polluted air may incr ease biomarkers of inflammation in mouse brain. Neurotoxicology 2005, 26, 133–140.

110. Fonken, L.K.; Xu, X.; Weil, Z.M.; Chen, G.; Sun, Q.; Rajagopalan, S. Air pollution impairs cognition, provokes depressiv e-like behaviors and alters hippocampal cytokine expression and morphology. Mol. Psychiatr. 2011, 16, 987–995.

111. Bhatt, D.P.; Puig, K.L.; Gorr, M.W.; Wold, L.E.; Combs, C.K. A pilot study to assess effects of long-term inhalation of air borne particulate matter on early Alzheimer-like changes in the mouse brain. PLoS ONE 2015, 10, e0127102.

112. Durga, M.; Devasena, T.; Rajasekar, A. Determination of LC50 and sub-chronic neurotoxicity of diesel exhaust nanopar ticles. Environ. Toxicol. Pharmacol. 2015, 40, 615–625.

113. Levesque, S.; Surace, M.J.; McDonald, J.; Block, M.L. Air pollution & the brain: Subchronic diesel exhaust exposure ca uses neuroinflammation and elevates early markers of neurodegenerative disease. J. Neuroinflamm. 2011, 8, 105.

114. Kim, S.H.; Knight, E.M.; Saunders, E.L.; Cuevas, A.K.; Popovech, M.; Chen, L.C. Rapid doubling of Alzheimer's amyloi d-β40 and 42 levels in brains of mice exposed to a nickel nanoparticle model of air pollution. F1000Research 2012, 1, 70.

115. Calderón-Garcidueñas, L.; Jewells, V.; Galaz-Montoya, C.; van Zundert, B.; Pérez-Calatayud, A.; Ascencio-Ferrel, E. In teractive and additive influences of gender, BMI and Apolipoprotein 4 on cognition in children chronically exposed to hig h concentrations of PM2.5 and ozone. APOE 4 females are at highest risk in Mexico City. Environ. Res. 2016, 150, 411 –422.

116. Schikowski, T.; Vossoughi, M.; Vierkötter, A.; Schulte, T.; Teichert, T.; Sugir, D. Association of air pollution with cognitive functions and its modification by APOE gene variants in elderly women. Environ. Res. 2015, 142, 10–16.

117. Kinney, J.W.; Bemiller, S.M.; Murtishaw, A.S.; Leisgang, A.M.; Salazar, A.M.; Lamb, B.T. Inflammation as a central mec hanism in Alzheimer's disease. Alzheimer's Dementia Transl. Res. Clin. Interv. 2018, 4, 575–590.

118. Morgan, B.P. Complement in the pathogenesis of Alzheimer's disease. Semin. Immunopathol. 2018, 40, 113–124.

119. Shi, Q.; Chowdhury, S.; Ma, R.; Le, K.X.; Hong, S.; Caldarone, B.J.; Stevens, B.; Lemere, C.A. Complement C3 deficie ncy protects against neurodegeneration in aged plaque-rich APP/PS1 mice. Sci. Transl. Med. 2017, 9, eaaf6295.

120. Zhu, C.B.; Blakely, R.D.; Hewlett, W.A. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alph a activate serotonin transporters. Neuropsychopharmacology 2006, 31, 2121–2131.

121. Metaxas, A.; Anzalone, M.; Vaitheeswaran, R.; Petersen, S.; Landau, A.M.; Finsen, B. Neuroinflammation and amyloid- beta 40 are associated with reduced serotonin transporter (SERT) activity in a transgenic model of familial Alzheimer's disease. Alzheimer's Res. Ther. 2019, 11, 1–13.

122. Ledo, J.H.; Azevedo, E.P.; Beckman, D.; Ribeiro, F.C.; Santos, L.E.; Razolli, D.S.; Kincheski, G.C.; Melo, H.M.; Bellio, M.; Teixeira, A.L.; et al. Cross talk between brain innate immunity and serotonin signaling underlies depressive-like beh avior induced by Alzheimer's amyloid-β oligomers in mice. J. Neurosci. 2016, 36, 12106–12116.

123. Elsworthy, R.J.; Aldred, S. Depression in Alzheimer's disease: An alternative role for selective serotonin reuptake inhibit ors? J. Alzheimer's Dis. 2019, 69, 651–661.

124. Caraci, F.; Copani, A.; Nicoletti, F.; Drago, F. Depression and Alzheimer's disease: Neurobiological links and common p harmacological targets. Eur. J. Pharmacol. 2010, 626, 64–71.

125. Cirrito, J.R.; Disabato, B.M.; Restivo, J.L.; Verges, D.K.; Goebel, W.D.; Sathyan, A.; Hayreh, D.; D'Angelo, G.; Benzing er, T.; Yoon, H.; et al. Serotonin signaling is associated with lower amyloid-β levels and plaques in transgenic mice and humans. Proc. Natl. Acad. Sci. USA 2011, 108, 14968–14973.

126. Claeysen, S.; Bockaert, J.; Giannoni, P. Serotonin: A new hope in Alzheimer's disease? ACS Chem. Neurosci. 2015, 6, 940–943.

127. Šimić, G.; Babić Leko, M.; Wray, S.; Harrington, C.R.; Delalle, I.; Jovanov-Milošević, N.; Bažadona, D.; Buée, L.; de Sil va, R.; Di Giovanni, G.; et al. Monoaminergic neuropathology in Alzheimer's disease. Prog. Neurobiol. 2017, 151, 101– 138.

128. Smith, G.S.; Barrett, F.S.; Joo, J.H.; Nassery, N.; Savonenko, A.; Sodums, D.J.; Marano, C.M.; Munro, C.A.; Brandt, J.; Kraut, M.A.; et al. Molecular imaging of serotonin degeneration in mild cognitive impairment. Neurobiol. Dis. 2017, 105, 33–41.

129. Kim, J.S.; Choi-Kwon, S. Poststroke depression and emotional incontinence: Correlation with lesion location. Neurology 2000, 54, 1805–1810.

130. Kim, J.S. Serotonin and stroke. In Handbook of Behavioral Neuroscience; Müller, C.P., Cunningham, K.A., Eds.; Elsevier: Amsterdam, The Netherlands, 2020; Volume 31, pp. 989–1000.

131. Lee, E.; Oh, M.; Kim, J.S.; Chang, D.I.; Park, J.H.; Cha, J.K.; Heo, J.H.; Sohn, S.I.; Kim, D.E.; Kim, H.Y.; et al. Serotonin transporter gene polymorphisms may be associated with poststroke neurological recovery after escitalopram use. J. Neurol. Neurosurg. Psychiatry 2018, 89, 271–276.

132. Monaco, F.; Fumero, S.; Mondino, A.; Mutani, R. Plasma and cerebrospinal fluid tryptophan in multiple sclerosis and degenerative diseases. J. Neurol. Neurosurg. Psychiatry 1979, 42, 640–641.

133. Tagliamonte, A.; Biggio, G.; Vargiu, L.; Gessa, G.L. Free tryptophan in serum controls brain tryptophan level and serotonin synthesis. Life Sci. II 1973, 12, 277–287.

134. Andersen, O.; Johansson, B.B.; Svennerholm, L. Monoamine metabolites in successive samples of spinal fluid. Acta Neurol. Scand. 1981, 63, 247–254.

135. Mostert, J.P.; Admiraal-Behloul, F.; Hoogduin, J.M.; Luyendijk, J.; Heersema, D.J.; van Buchem, M.A.; De Keyser, J. Effects of fluoxetine on disease activity in relapsing multiple sclerosis: A double-blind, placebo-controlled, exploratory study. J. Neurol. Neurosurg. Psychiatry 2008, 79, 1027–1031.

136. Mohr, D.C.; Boudewyn, A.C.; Goodkin, D.E.; Bostrom, A.; Epstein, L. Comparative outcomes for individual cognitive-behavior therapy, supportive-expressive group psychotherapy, and sertraline for the treatment of depression in multiple sclerosis. J. Consult. Clin. Psychol. 2001, 69, 942–949.

137. Grech, L.B.; Butler, E.; Stuckey, S.; Hester, R. Neuroprotective benefits of antidepressants in multiple sclerosis: Are we missing the mark? J. Neuropsy. Clin. Neurosci. 2019, 31, 289–297.

138. Honoré, P.J.; Deianova, N.; Loret, G.; Hemelsoet, D. An easily overlooked cause of toxic encephalopathy: Methylene blue in a patient on an SSRI. Acta Neurol. Belg. 2018, 118, 121–122.

139. Otte, C.; Gold, S.M.; Penninx, B.W.; Pariante, C.M.; Etkin, A.; Mohr, D.C.; Schatzberg, A.F. Major depressive disorder. Nat. Rev. Dis. Primers 2016, 2, 16065.

140. Hirschfeld, R.M. History and evolution of the monoamine hypothesis of depression. J. Clin. Psychiatry 2000, 61, 4–6.

141. Underwood, M.D.; Kassir, S.A.; Bakalian, M.J.; Galfalvy, H.; Dwork, A.J.; Mann, J.J.; Arango, V. Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. Transl. Psychiatry 2018, 8, 279.

142. Yohn, C.N.; Gergues, M.M.; Samuels, B.A. The role of serotonin receptors in depression. Mol. Brain 2017, 10, 28.

143. Van den Bosch, M.; Meyer-Lindenberg, A. Environmental exposures and depression: Biological mechanisms and epidemiological evidence. Annu. Rev. Public Health 2019, 40, 239–259.

144. Lee, K.S.; Lim, Y.H.; Kim, K.N.; Choi, Y.H.; Hong, Y.C.; Lee, N. Urinary phthalate metabolites concentrations and symptoms of depression in an elderly population. Sci. Total Environ. 2018, 625, 1191–1197.

145. Shiue, I. Urinary heavy metals, phthalates and polyaromatic hydrocarbons independent of health events are associated with adult depression: USA NHANES, 2011–2012. Environ. Sci. Pollut. Res. 2015, 22, 17095–17103.

146. Roberts, S.; Arseneault, L.; Barratt, B.; Beevers, S.; Danese, A.; Odgers, C.L.; Moffitt, T.E.; Reubeng, A.; Kelly, F.J.; Fisher, H.L. Exploration of NO2 and PM2.5 air pollution and mental health problems using high-resolution data in London-based children from a UK longitudinal cohort study. Psychiatry Res. 2019, 272, 8–17.

147. Xin, F.; Fischer, E.; Krapp, C.; Krizman, E.N.; Lan, Y.; Mesaros, C.; Snyder, N.W.; Bansal, A.; Robinson, M.B.; Simmons, R.A.; et al. Mice exposed to bisphenol A exhibit depressive-like behavior with neurotransmitter and neuroactive steroid dysfunction. Horm. Behav. 2018, 102, 93–104.

148. Mokoena, M.L.; Harvey, B.H.; Viljoen, F.; Ellis, S.M.; Brink, C.B. Ozone exposure of Flinders Sensitive Line rats is a rodent translational model of neurobiological oxidative stress with relevance for depression and antidepressant response. Psychopharmacology 2015, 232, 2921–2938.