and Greene, 1978; Purkerson-Parker et al., 2001; Hatcher et al., 2007), and in primary mesencephalic cultures or dopaminergic cell lines (0.01–300 μM) (Sanchez-Ramos et al., 1998; Kitazawa et al., 2001, 2003; Kanthasamy et al., 2005). Aggregation of α–syn, ubiquitin–proteasome impairment function (Uversky et al., 2001; Sun et al., 2005) and microglia activation (Mao and Liu, 2008) have also been observed.

Paraquat is a quaternary nitrogen herbicide used worldwide. Due to its structural similarity to MPP (the active metabolite of MPTP), it was thought to be toxic to dopaminergic neurons and thus might be related to PD. The possible association between PQ and PD received attention from the study of Liou et al. (1997) performed in PD patients (120 patients and 240 controls) in Taiwan, in which the pesticide use was associated with an increased risk of developing PD, being higher for those individuals who reported using PQ (Liou et al., 1997). Likewise, Tanner et al. (2011) reported a significant association between PD and the use of oxidative pesticides, including PQ (OR = 2.5, 95% CI, 1.4–4.7) in professional pesticide applicators (110 cases and 358 controls) (Tanner et al., 2011). Similarly, other epidemiologic studies have associated the exposure to PQ with PD (Hertzman et al., 1990; Ascherio et al., 2006; Kamel et al., 2007; Wang et al., 2011).

Paraquat is taken up into dopaminergic terminals by the dopamine transport and organic cation transporter 3 (Rappold et al., 2011), and causes cellular toxicity by oxidative stress through the cellular redox cycling generating superoxide radical by the oxidation of NADPH, which in turn impairs the restauration of GSH levels and thus the activity of several antioxidant systems (Berry et al., 2010; Franco et al., 2010). It has been observed that repeated administrations of PQ to adult mice and rats (5–10 mg/Kg/ week/at least 3 weeks, i.p.) increase ROS levels in the striatal homogenate, induce a dose-dependent decrease in dopaminergic neurons from the substantia nigra, a decline in striatal dopamine nerve terminal density, and a neurobehavioral syndrome characterized by reduced ambulatory activity (Brooks et al., 1999; McCormack et al., 2002; Kuter et al., 2010). PQ also reproduces other biochemical and neuropathological characteristics of human Parkinsonism such as microglia activation (Wu et al., 2005; Purisai et al., 2007), α-syn up-regulation and fibrillation (Uversky et al., 2001; Manning-Bog et al., 2002), increases lipid peroxidation (increase of 4-hydroxynonenals) (McCormack et al., 2005), alters parkin solubility promoting its intracellular aggregation (Wang et al., 2005), induces a proteasome dysfunction in SH-SY5Y cells (Ding and Keller, 2001; Yang and Tiffany-Castiglioni, 2007), as well as in homogenates from postmortem PD brains (McNaught and Jenner, 2001; McNaught et al., 2002), impairs mitochondrial function at the level of complex III to generate ROS (Castello et al., 2007; Drechsel and Patel, 2009), promotes cytochrome *C* release (González-Polo et al., 2004; Fei et al., 2008), induces GSH depletion (Schmuck et al., 2002; Kang et al., 2009), and causes cell injury leading to apoptotic cell death (Berry et al., 2010; Franco et al., 2010). PQ has been used as a toxicological model for PD that has permitted getting important information about the mechanisms involved in the neurodegeneration associated with PD (Gao and Hong, 2011).

Rotenone, an OP insecticide has also been associated with an increased risk of PD. Two epidemiological studies found an association between rotenone exposure and PD risk, reporting an increased risk of 10–fold (OR = 10.0, 95% CI, 2.9–34.3) in East Texas farmers (Dhillon et al., 2008), and 2.5-fold (OR = 2.5, 95% CI, 1.3–4.7) in PD cases (n = 110) compared with controls (n = 358) from professional pesticide applicators participants in the AHS (Tanner et al., 2011). Rotenone can freely cross the blood–brain barrier and is a well-established mitochondrial toxin that specifically inhibits the complex I (NADH–dehydrogenase) of the electron transport chain leading to ATP depletion, energy failure and mitochondrial ROS production, which in turn induces cytochrome *C* release and apoptotic cell death (Clayton et al., 2005; Radad et al., 2006; Sherer et al., 2007). It has been shown that, like MPTP, rotenone treatment in animal models (1.5–3 mg/Kg/day/up to 3 weeks) reproduces features of PD such as bradykinesia, postural instability and/or rigidity, reduces the tyrosine hydroxylase-positive neurons in the substance nigra, induces a loss of striatal dopamine, and the accumulation of α-syn and poly-ubiquitin positive aggregates in remaining dopaminergic neurons (Betarbet et al., 2000; Sherer et al., 2003; Cannon et al., 2009). Likewise, Betarbet et al. (2006) observed that chronic administration of 3.0 mg/Kg/day of rotenone for up to 5 weeks to male rats caused the oxidation of DJ-1, accumulation of α-syn, and proteasomal impairment (Betarbet et al., 2006). These effects were also observed in neuroblastoma SK-N-MC cells treated with rotenone (5 nM/4 weeks), as well as a loss of GSH, oxidative DNA and protein damage and caspase-dependent death (Sherer et al., 2002; Betarbet et al., 2006). Rotenone has also the capacity to activate microglia (Sherer et al., 2003); Gao et al. (2002) demonstrated that the addition of microglia to primary neuron-enriched cultures (neuron/glia cultures) markedly increased the dopaminergic neurodegeneration induced by rotenone (1 nM/8 days), and this neurotoxicity was attenuated by the inhibition of NADPH oxidase or scavenging the superoxide radical that is liberated from the microglia (Gao et al., 2002). Since rotenone recapitulates several mechanisms of PD pathogenesis, this pesticide is currently used as a toxicological model to study the underlying mechanisms on the PD development.

Despite the widespread use of OP insecticides such as malathion, methyl parathion, chlorpyriphos and diazinon, not many studies have evaluated the association between specific OP and PD risk. Dhillon et al. (2008) found a 2–fold increase (OR = 2.0, 95% CI, 1.02–3.8) in the risk of PD in Texan agricultural workers exposed to chlorpyriphos (cases = 100, controls = 84) (Dhillon et al., 2008). An increased risk of PD was also observed in rural residents from California possibly exposed to high levels of chlorpyriphos (OR = 1.87, 95% CI, 1.05–3.31) and diazinon (OR = 1.75, 95% CI, 1.12–2.76) through the consumption of contaminated well–water (Gatto et al., 2009). One study conducted in a population from the Group Health Cooperative (GHC) in Western Washington State occupationally exposed to methyl parathion found a high risk of PD (OR = 8.08, 95% CI, 0.92–70.85), although the association was not statistically significant (Firestone et al., 2005). This is particularly relevant,

because parkinsonian effects have been reported in cases of patients intoxicated with OP (Bhatt et al., 1999).

Solvents

Solvents are widespread used due to their commercial applications, including metal degreasing, dry cleaning, and as ingredients of paint thinners and detergents. Some solvents are lipophilic and thus easily absorbed by the central and peripheral nervous system tissues (Lock et al., 2013). There are isolated cases of acute Parkinsonism associated with large solvent exposures such as in workers exposed to *n*-hexane (Pezzoli et al., 1989), and toluene (Papageorgiou et al., 2009), among others. There is no consistent evidence of the association of solvent exposure and PD (Wirdefeldt et al., 2011). One case-control study based on a questionnaire reported an increased risk of PD by the exposure to organic solvents (OR = 2.78, 95% CI, 1.23–6.26) in 86 PD patients and 86 controls from the Emilia-Romagna region in Italy (Smargiassi et al., 1998). Another case–control study reported an increased risk of PD when the exposure to solvents was above 20 years (OR = 3.59, 95% CI, 1.26–19.26) in 182 cases (vs. 422 controls) identified through death certificates of the Rolls-Royce PLC national pension fund archive from employees of five manufacturing locations in United Kingdom who had any mention of PD (McDonnell et al., 2003).

Trichloroethylene (TCE) is one of the specific solvents that has been investigated in detail (Goldman, 2014). Some clinical case reports have reported the onset of PD in workers exposed to TCE through chronic inhalation and dermal exposure by handling TCE, suggesting a potential link between the exposure to TCE and PD (Kochen et al., 2003; Gash et al., 2008). More recently, an epidemiologic study in 99 twin pairs discordant for PD showed that the exposure to TCE was associated with a 6–fold increased risk of PD (OR = 6.1, 95% CI, 1.2–33) (Goldman, 2014). In animal models, TCE may recapitulate several key pathological features of PD. The systemic exposure of adult rats to TCE (1000 mg/Kg/day/5 days a week/2 and 6 weeks, oral gavage) inhibits mitochondrial complex I enzyme activity, increases oxidative stress markers, activates the microglia, induces nigral α-syn accumulation and a significant loss of dopaminergic neurons on the SNpc in a dose-dependent manner, as well as defects in the rotarod behavior test (Liu et al., 2010). In a similar way, the administration of *n*-hexane and its metabolite 2, 5-hexanedione (400 mg/Kg/day/5 days a week/6 weeks, i.p.) to mice caused that both chemicals reduced the striatal dopamine concentration by 38 and 33%, respectively, but neuronal cell loss was not confirmed (Pezzoli et al., 1990). On the other hand, there is no evidence that acute or subchronic exposure to toluene promotes the degeneration of the nigrostriatal dopamine system (Lock et al., 2013).

Nanoparticles and PD

Nanoparticles are an important alternative in the development of treatment strategies for neurodegenerative diseases due to their small particle size, large surface and high drug loading efficiency, which allow them to cross the blood-brain barrier and efficiently release specific drugs (Li et al., 2014b; Leyva-Gómez et al., 2015). However, their small size allows them to penetrate the cell and organelles, disrupting their normal function (Buzea et al., 2007).

Although some NPs are being used in therapies for PD, no epidemiological studies are available associating them with PD risk. However, there is evidence suggesting that they could contribute to alter the molecular mechanisms involved in the pathogenesis of PD. Thus, it was reported that intranasal instillation of SiO_2-NPs (20 μg/day/1–7 days) to rats resulted in their presence in the striatum, the induction of oxidative damage, an inflammatory response, and depleted dopamine concentration and tyrosine hydroxylase levels, suggesting that these NPs have a negative impact on striatal dopaminergic neurons (Wu et al., 2011). Another report in adult zebrafish exposed to SiO_2-NPs (300 and 1000 μg/mL; 15 and 50-nm of size) showed alterations in neurobehavioral parameters (general, cognitive behavior and locomotive activity), with the most significant effects observed with the smallest NPs, similar to those observed in neurodegenerative diseases (Li et al., 2014b). *In vitro* studies also support the potential contribution of NPs in PD development. The exposure of dopaminergic neurons (PC12 cells) to SiO_2-NPs (25–200 μg/mL/24 h) triggered an oxidative stress, disturbed the cell cycle, induced apoptosis, and activated the p53-mediated signaling pathway (Wu et al., 2011); while the exposure of these cells to TiO_2-NPs (50, 100 and 200 mg/mL/24 h) induced a dose–dependent increase in the expression and aggregation of α-syn, as well as a reduction of the expressions of *Parkin* (E3 ligase), and the ubiquitin C-terminal hydrolase (*UCH-L1*), these events were associated with increased oxidative stress (Wu and Xie, 2014). Also, the exposure PC12 cells to iron oxide (Fe_2O_3-NPs; 0.15–15 mM) decreased the neurite growth in response to the nerve growth factor (NGF) (Pisanic et al., 2007). Likewise, citrate-capped gold nanoparticles (Au-NPs; 0.3–32 nM, 10–22 nm) produced a dose-dependent aggregation of purified α-syn, being strongest for the smallest NPs (Alvarez et al., 2013). In contrast, the administration of Neurotensin (NTS)-polyplex NPs (8.5 nmol/Kg, i.v), a nanocarrier gene with a potential for nanomedicine-based applications for PD treatment, to BALB/c mice does not produce systemic inflammatory (up to 24 h after treatment) nor hepatic cytotoxicity (at 24 and 96 h after treatment), supporting the safety of these NTS-polyplex NPs as a potential therapeutic approach (Hernandez et al., 2014).

Early Exposure to Environmental Factors and AD or PD Development: Epigenetic Evidence

Epigenetic DNA modifications include DNA methylation, histone post-translational modifications (mainly acetylation) and miRNAs (Holliday, 2006). DNA methylation is one of the most studied epigenetic modifications that influence the gene expression. It involves the addition of methyl groups to cytosine bases located at cytosine–phosphate–guanine (CpG) sites by the action of DNA methyltransferases (DNMTs). Alterations in DNA methylation on the promoter regions of genes regulate the gene expression of important processes such as embryonic development, cellular differentiation and aging (Bird, 2002). Increasing evidence suggests that epigenetic changes in the developing embryo that may play important roles in

the susceptibility to diseases in later life (imprinted disease phenotypes) result from maternal exposures to environmental stimuli at critical periods of development. This suggests that a short exposure to chemicals could be memorized through epigenetic mechanisms long after the chemical trigger has gone (Jang and Serra, 2014), and recent studies have suggested that an epigenetic component could be involved in neurodegenerative diseases related to environmental factors (Marques et al., 2011).

The latent brain expression of genes observed in animals developmentally exposed to an environmental contaminant may be mediated through epigenetic pathways that are regulated via the DNA methylation. While the conditions leading to early life hypo- or hyper-methylation of specific genes are not known, both can induce oxidative DNA damage; for instance the hypo-methylation of *APP* gene increases its expression driving the overproduction of APP and Aβ levels, which in turn facilitate the ROS production damaging the DNA, and producing neuronal loss. While the hyper-methylation affects the gene transcription and DNA repair pathways. Therefore, both changes in DNA methylation can impact gene expression and imprint susceptibility to oxidative DNA damage in the aged brain (Zawia et al., 2009). Thus, it is suggested that Pb interferes with the DNA methylating capacity, thus altering the expression of AD-related genes. The study performed in aged monkeys developmentally exposed to Pb revealed a reduced activity of brain Dnmt, and the exposure of mouse primary cells from the cerebral cortex to Pb (0.1 μM) resulted in a similar effect on Dnmt1 activity a week after 24 h-treatment (Wu et al., 2008). Also, Bihaqi and Zawia (2012) showed a significant latent increase in AD biomarkers an a reduction in the protein and mRNA levels of DNA methylating enzymes Dnmt1 and Dnmt3a, and methyl CpG binding protein 2 (MeCP2) in differentiated SH-SY5Y cells treated with Pb (5–100 μM/48 h) and analyzed 6 days later (Bihaqi and Zawia, 2012). Aberrant CpG methylation in *APP*, *Tau* and *GSK3*β genes was reported in post-mortem brains (Iwata et al., 2014). In addition, it suggested that reduced levels of CpG methylation in the promoter of *APP* could be mediated by the oxidation of guanine (8-oxdG) (Zawia et al., 2009); this is because the oxidation of guanine in CpG dinucleotides inhibits adjacent cytosine methylation (Weitzman et al., 1994). On the other hand, Cd, another metal involved in AD pathology, reduces the enzymatic activity of Dnmt in rat liver cell cultures (Poirier and Vlasova, 2002), but this effect has not been evaluated in cerebral cells. While a study showed that subchronic As exposure (3 and 36 ppm/from gestation until 4 months of age) altered the methylation of genes involved in neuronal plasticity, including reelin (RELN) and protein phosphatase 1 (PP1), which was associated with memory deficits (Martínez et al., 2011). Regarding other compounds, the perinatal exposure to permethrin (34 mg/Kg/daily, by gavage from postnatal day 6–21) to mice showed altered brain functions including biomarkers of maintenance of dopaminergic neurons, and impairment of spatial memory at 6 months of age (Nasuti et al., 2013).

The relation between epigenetic modifications and PD has been less studied; however, a potential role of DNA methylation in the promoter of α-syn encoding gene (*SNCA*) in the neuropathogenesis of PD has been suggested, considering that α-syn is a fundamental component of LB, the main hallmark of PD (Lu et al., 2013). A DNA hypomethylation of *SNCA* was reported in the substantia nigra of sporadic PD patients, suggesting that it might contribute to the dysregulation of *SNCA* expression in PD (Jowaed et al., 2010; Matsumoto et al., 2010). In addition, increased *SNCA* mRNA levels were observed in SNpc of PD (Chiba-Falek et al., 2006), and reduced levels of Dnmt1 have been observed in postmortem brains from PD and dementia with LB (DLB) patients, as well as in brains of α-syn transgenic mice; authors suggest that this effect could be a novel mechanism of epigenetic dysregulation in LB-related diseases such as PD (Desplats et al., 2011). Finally, a lesser degree of methyation of the *TNF*α promoter, a key inflammatory cytokine associated with dopaminergic cell death was observed in the SNpc from PD patients, predisposing to an increase neuronal vulnerability to inflammatory reactions (Mogi et al., 1996; Pieper et al., 2008).

Environmental factors associated with an increased risk of PD such as pesticides can alter the expression of genes by epigenetic mechanisms (Kwok, 2010). It was reported that pre-treatment with 5-aza-2'deoxycytidine (5'-aza-dC, a DNMT inhibitor) exacerbated the dopaminergic neuron damage induced by PQ, MPP^+, 6-hydroxydopamine (6-OHDA) and rotenone treatment, and induced oxidative stress, the transcriptional up-regulation of α-syn, and demethylation of the α-syn promoter (Wang et al., 2013). Likewise, the folate deficiency sensitizes mice to MPTP-induced PD-like pathology and motor dysfunction (Duan et al., 2002); it is well known that folate deficiency alters the development of human nervous system (Greenblatt et al., 1994).

On the other hand, it was reported that the exposure to environmental neurotoxicants associated with PD during early life or pregnancy can determine the progressive damage of the substantia nigra years before the onset of clinical parkinsonism, as well as to increase the vulnerability to effects of a second environmental factor (two–hit model) (Logroscino, 2005). A study in C57BL/6 mice daily treated with pQ (0.3 mg/Kg) or maneb (1 mg/Kg) or PQ + maneb from postnatal day 5–19 and then re-exposed as adults to PQ (10 mg/Kg) or maneb (30 mg/Kg) or PQ + maneb (twice a week/3 weeks) showed that dopaminergic cell loss and decreased dopamine levels were amplified by the adult re-challenge to the pesticides, suggesting that the developmental exposure to neurotoxins enhanced the adult susceptibility to a new toxic insult (Thiruchelvam et al., 2002). Similarly, prenatal exposure of pregnant C57BL/6J mice to PQ (0.3 mg/Kg) or maneb (1 mg/Kg) altered the development of the nigrostriatal system and enhanced its vulnerability to neurotoxins later in life, which could contribute with the development of PD during aging (Barlow et al., 2004).

Although there is no direct evidence linking early exposure to environmental pollutants and epigenetic changes with increased susceptibility to LOPD, there is a plausible association based on the following considerations: (1) epigenetic alterations have been observed in PD brains; (2) the exposure to environmental factors is associated with an increased risk of LOPD development and factors such as pesticides and metals can alter mechanisms of epigenetic regulation such as DNA methylation; and (3) early

exposure to environmental pollutants might be associated with LOPD later in life. Further studies are needed to confirm this hypothesis in this promising research field to understand the mechanisms underlying the long-term effects of the environment on the PD development.

Concluding Remarks

The emerging association between exposures to several toxic compounds with neurodegenerative diseases is of considerable public health importance, given the increasing dementia prevalence, the negative social and economic consequences of neurodegeneration-related disabilities, and the increasing environmental pollution in some geographic areas worldwide. Some of the epidemiological studies show not consistent results on getting significant estimates of hazard risk for AD or PD, mainly due to some limitations that include the difficulty on accurate diagnosis for AD or PD cases due to the lack of specific biomarkers, the deficiency to accurately assess chronic exposures, and/or the lack of inclusion of important confounding variables such as co-exposure to toxic compounds, genetic variants and lifestyle among others. Nevertheless, epidemiological studies along with experimental data have led to highlight the potential risk to develop these degenerative diseases due to the exposure to environmental pollutants such as metals, NPs and pesticides, among others. Interestingly, these pollutants show similar mechanisms of toxicity, which converge in a generalized mechanism based on the generation of oxidative stress that leads to common hallmarks of both neurodegenerative disorders. For example, the generation of oxidative stress by increasing the production of ROS and/or deregulating the antioxidant enzymes promotes the formation of protein aggregates such as Tau, Aβ or α-syn. This in turn overwhelms the degradation systems, and produces the activation of the glia inducing neuroinflammation, a process that *per se* increases the generation of further oxidative stress leading to a self-perpetuating cycle, and finally to neuronal loss of specific brain region such as the hippocampus and cerebral cortex in AD and substantia nigra in PD. The oxidative stress induced by these neurotoxicants activates/inhibits signaling pathways leading to augmented/diminished activity of enzymes that promote the accumulation of toxic materials in neural cells such as damaged/aberrant proteins, Aβ in AD or α–syn in PD and oxidative byproducts, or the oxidation of DNA that can alter genetic or epigenetic regulation. Furthermore, the link between early life exposure to environmental factors and the origin of neurodegenerative diseases is getting attention and can help to clarify the role of the environment on the development of these degenerative diseases. On the other hand, the lack of specific/differential biomarkers for AD or PD limits the early diagnosis and then the timely treatment. In this regard, specific circulating miRNAs have been associated with pathological processes such as AD and PD, therefore they are promising non-invasive biomarkers for these neurological diseases. Additionally, the identification of biomarkers to determine the past exposure to environmental pollutants is of vital importance for a better and opportune management of these diseases. Thus, as we have more knowledge of the risk from the exposure to environmental pollutants, more well-designed epidemiological studies (controlling for as many variables as possible and with high sample sizes) are necessary to improve the quality of life of elderly and to prevent the development of neurodegenerative diseases worldwide.

References

Abbott, R. D., Ross, G. W., Tanner, C. M., Andersen, J. K., Masaki, K. H., Rodriguez, B. L., et al. (2012). Late-life hemoglobin and the incidence of Parkinson's disease. *Neurobiol. Aging* 33, 914–920. doi: 10.1016/j.neurobiolaging.2010.06.023

Altmann, P., Cunningham, J., Dhanesha, U., Ballard, M., Thompson, J., and Marsh, F. (1999). Disturbance of cerebral function in people exposed to drinking water contaminated with aluminium sulphate: retrospective study of the Camelford water incident. *BMJ* 319, 807–811. doi: 10.1136/bmj.319.7213.807

Alvarez, Y. D., Fauerbach, J. A., Pellegrotti, J. V., Jovin, T. M., Jares-Erijman, E. A., and Stefani, F. D. (2013). Influence of gold nanoparticles on the kinetics of alpha-synuclein aggregation. *Nano Lett.* 13, 6156–6163. doi: 10.1021/nl403490e

An, L., Liu, S., Yang, Z., and Zhang, T. (2012). Cognitive impairment in rats induced by nano-CuO and its possible mechanisms. *Toxicol. Lett.* 213, 220–227. doi: 10.1016/j.toxlet.2012.07.007

Ascherio, A., Chen, H., Weisskopf, M. G., O'Reilly, E., McCullough, M. L., Calle, E. E., et al. (2006). Pesticide exposure and risk for Parkinson's disease. *Ann. Neurol.* 60, 197–203. doi: 10.1002/ana.20904

Ashok, A., Rai, N. K., Tripathi, S., and Bandyopadhyay, S. (2015). Exposure to As-, Cd- and Pb-mixture induces Aβ, amyloidogenic APP processing and cognitive impairments via oxidative stress-dependent neuroinflammation in young rats. *Toxicol. Sci.* 143, 64–80. doi: 10.1093/toxsci/kfu208

Atwood, C. S., Moir, R. D., Huang, X., Scarpa, R. C., Bacarra, N. M., Romano, D. M., et al. (1998). Dramatic aggregation of Alzheimer abeta by Cu(II) is induced by conditions representing physiological acidosis. *J. Biol. Chem.* 273, 12817–12826. doi: 10.1074/jbc.273.21.12817

Baldi, I., Lebailly, P., Mohammed-Brahim, B., Letenneur, L., Dartigues, J. F., and Brochard, P. (2003). Neurodegenerative diseases and exposure to pesticides in the elderly. *Am. J. Epidemiol.* 157, 409–414. doi: 10.1093/aje/kwf216

Barlow, B. K., Richfield, E. K., Cory-Slechta, D. A., and Thiruchelvam, M. (2004). A fetal risk factor for Parkinson's disease. *Dev. Neurosci.* 26, 11–23. doi: 10.1159/000080707

Basha, M. R., Wei, W., Bakheet, S. A., Benitez, N., Siddiqi, H. K., Ge, Y. W., et al. (2005). The fetal basis of amyloidogenesis: exposure to lead and latent overexpression of amyloid precursor protein and beta-amyloid in the aging brain. *J. Neurosci.* 25, 823–829. doi: 10.1523/jneurosci.4335-04.2005

Basun, H., Forssell, L. G., Wetterberg, L., and Winblad, B. (1991). Metals and trace elements in plasma and cerebrospinal fluid in normal aging and Alzheimer's disease. *J. Neural Transm. Park. Dis. Dement. Sect.* 3, 231–258.

Baum, L., Chan, I. H., Cheung, S. K., Goggins, W. B., Mok, V., Lam, L., et al. (2010). Serum zinc is decreased in Alzheimer's disease and serum arsenic correlates positively with cognitive ability. *Biometals* 23, 173–179. doi: 10.1007/s10534-009-9277-5

Behl, M., Zhang, Y., Monnot, A. D., Jiang, W., and Zheng, W. (2009). Increased β-amyloid levels in the choroid plexus following lead exposure and the involvement of low-density lipoprotein receptor protein-1. *Toxicol. Appl. Pharmacol.* 240, 245–254. doi: 10.1016/j.taap.2009.05.024

Behl, M., Zhang, Y., Shi, Y., Cheng, J., Du, Y., and Zheng, W. (2010). Lead-induced accumulation of beta-amyloid in the choroid plexus: role of low