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Review

Anthropogenic pollutants may increase the incidence of neurodegenerative disease in an aging population

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Abstract

The current world population contains an ever-increasing increased proportion of the elderly. This is due to global improvements in medical care and access to such care. Thus, a growing incidence of age-related neurodegenerative disorders is to be expected. Increased longevity also allows more time for interaction with adverse environmental factors that have the potential exert a gradual pressure, facilitating the onset of organismic aging. Nearly all neurodegenerative disorders have a relatively minor genetic element and a larger idiopathic component. It is likely that some of the unknown factors promoting neurological disease involve the appearance of some deleterious aspects of senescence, elicited prematurely by low but pervasive levels of toxic materials present in the environment. This review considers the nature of such possible toxicants and how they may hasten neurosenescence. An enhanced rate of emergence of normal age-related changes in the brain can lead to increased incidence of those specific neurological disorders where aging is an essential requirement. In addition, some xenobiotic agents appear to have the capability of engendering specific neurodegenerative disorders and some of these are also considered.

Keywords: Neurodegenerative disease; Oxidative stress; Free radicals; Inflammation; Antioxidants; Neurotoxic agents

1 Introduction

As life expectancy increases worldwide, the time available for extended exposures to toxic materials present in the environment is increased. By this means the continuous presence of low levels of xenobiotic agents can exert a subtle effect on the aging process. The interaction of neurotoxic chemicals with the normal aging process is difficult to detect, as it can be very slow and progressive. Epidemiological investigation can be an important tool but since it is performed over a prolonged period, is subject to a large range of extraneous confounders. Animal experimentation is also useful but models of human aging are incomplete and extended low level dosing is expensive to carry out as well as also being subject to irrelevant factors. These difficulties should not negate the growing importance of this area of study. This review is intended to document some agents that may synergize with normal senescence and bring about a premature decline in optimal health. Many neurological diseases are found only with maturation or aging. Multiple sclerosis (MS), Huntingdon's disease (HD), amyotrophic lateral sclerosis (ALS) are associated with a relatively early stage of maturation while Alzheimer's disease (AD), Parkinson's disease (PD) generally occur at a later stage of aging. All of these disorders however, have in common that they are not found in childhood or in very young adults. The implication of this is that certain types of insufficiency can only be expressed in conjunction with a maturation/aging process. Thus aging plays a key role in enabling the emergence of these disorders. Once the aging process is under way it can permit the overt appearance of disease, which was previously only present in an occult form. Aging and maturation are thus essential platforms for the emergence of specific neurological diseases.

Some of these disorders have a clear genetic origin. For example HD is a genetic disorder, which has a 100% penetrance. Others have a marked genetic component but studies on identical twins indicate incomplete penetrance, e.g., familial AD and PD. However the great majority of cases of neurodegenerative disorders are of idiopathic causation. This suggests that they are likely to be initiated or promoted by exogenous environmental factors. In addition, it is likely that the velocity of normal aging can be modulated in the presence of various environmental xenobiotic chemicals.

1.1 Parkinson's disease

Idiopathic Parkinson's disease (PD) is a relatively common disorder of unknown cause, involving progressive loss of dopaminergic neurons ultimately leading to severe movement and postural deficits. There is no known cure for slowing the advancement of the disease. Although there are changes in several brain regions, the major symptoms of PD are attributable to the death of dopaminergic neurons in the substantia nigra and striatal structures. Due to their content of dopamine whose ready oxidation takes place by way of reactive oxidant intermediates, dopaminergic neurons are specifically susceptible to oxidative damage. Dopamine neurons are continually lost throughout the normal lifespan. Perhaps to compensate for their fragility, such neurons are present in striatal tissues in excess so that abnormalities in their circuitry with resulting behavioral inadequacies are not apparent until around 80% of neurons have been lost. It is likely that PD stems from a distinctive neuronal design, making its appearance

simply a matter of time (Surmeier, 2007).

Some neurotoxic agents have been shown to accelerate the normal age-related loss of dopamine neurons. This can lead to premature appearance of PD-like signs. The classical example of this is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) which can be a contaminant of illicitly manufactured Demerol-like compounds used as recreational drugs (Langston, 1996). This agent can pass through the blood brain barrier and is taken up by the high affinity uptake dopamine transporter of dopaminergic neurons and thus becomes greatly concentrated within such cells. It can than be oxidized to MPP^+ by monoamine oxidase B. This then leads to the generation of intense reactive oxygen species activity within the cell. The resulting damage to mitochondria may prove lethal to the cell. Such inadvertent exposure to MPTP has led to PD-like signs in young men aged under 25. While this is a rare and spectacular example of an acute response, it has led to a range of broader questions. Since PD can occur at any age over 40, this has raised the issue of whether early-onset PD may have an analogous origin, following lower and more prolonged exposure to unknown chemicals. The interaction of a toxicant with aging can take place at an early stage of the aging process. In view of the potentially long interval between an exposure and the appearance of deficits, such inferences are difficult to make with certainty. However, both epidemiological and laboratory evidence reveal that excess levels of dopaminergic damage or PD are associated with exposure to specific pesticides and other environmental contaminants including manganese, and heterocyclic amines with isoquinoline structures (Gorell et al., 2004). This association is strong enough to clearly demonstrate the environmental causation of a significant fraction of all PD cases.

Another factor relating to the environmental causation of PD concerns the reduced hepatic uptake and metabolism of toxic agents in aged animals. This has been reported for MPTP, paraquat and malathion (Yang et al., 2002) and could enhance the ability of low levels of these materials to effect death of dopaminergic neurons.

1.2 Alzheimer's disease

Alzheimer's disease (AD) is very prevalent among the elderly, the risk of incurring AD developing steadily with age. As with PD, it is suspected that if longevity were sufficient, the whole population would eventually succumb to AD. Also, as with PD, the bulk of AD incidence is idiopathic although clear genetically incurred risk factors are known. AD is largely associated with the selective death of cholinergic neurons, leading to profound deficits in intellectual function, especially those relating to memory and learning. While there is no acute exogenous exposure to a chemical that has led to AD-like changes in young humans, in a manner parallel to MPTP as an acute model for PD, some animal models reveal that a relatively minor loss of hippocampal cholinergic neurons can produce memorial shortcomings. Unlike the case for dopamine neurons, humans are not initially equipped with a large surplus of cholinergic neurons. This means that significant intellectual handicaps are apparent even with the death of only 5–10% of cholinergic nerve cells.

A considerable range of chemicals has been proposed as contributing to the initiation or progression of AD. These include excess levels of several metals. In the case of aluminum and copper there is both epidemiological and animal experimental evidence for the promotion of neuroinflammation that is also pronounced in AD (White et al., 2004; Becaria et al., 2006). Lead and mercury have also been implicated as enhancing AD development (Brewer, 2012; Maloney et al., 2012). Environmentally persistent organic compounds that may be implicated in AD pathogenesis include bisphenol A and phthalates and polynuclear aromatic hydrocarbons such as dioxins and polychlorinated biphenyls. Such lipophilic compounds can cross the blood brain barrier, are only slowly metabolized and eliminated and thus can gradually accumulate to reach neurotoxic levels. Epidemiological studies suggest that several forms of neurological derangement can ensue, including AD and PD as well as neurodevelopmental deficits (Zeliger, 2013)

1.3 Prion disease

Prion disease is caused by exposure to an abnormal variant of prion protein, which has the capability of altering the folding profile of normal prion protein to a form, which is not degraded by intracellular proteases. As catalytic conversion of normal non-pathological prion proteins progresses this indigestible material forms aggregates and kills the cell. Prion disease involves gliosis, the production of pro-inflammatory cytokines and neurodegeneration (Peyrin et al., 1999). Although this disease is rare in humans, it has been revealed to have broad ramifications and relevance. The misfolding and aggregation of specific proteins characterizes many neurodegenerative disorders. Such diseases now include AD, PD, HD and ALS. Normal brain aging is also associated with formation and accumulation of protein aggregates (Cuanalo-Contreras et al., 2013). The induction of aggregation involves a crystallization-like seeding mechanism by which a specific protein is structurally corrupted by its misfolded conformer. These misfolded proteins can spread from one site to another via cellular uptake and transport (Walker and LeVine, 2012). Aβ aggregates can also act as self-propagating catalysts in this manner (Stöhr et al., 2012).

Environmental factors that can initiate prion disease include beef consumption, organ transplants, pituitary hormone treatment, blood transfusion and corneal transplants and use of contaminated dental equipment. Parallel evidence suggests that abnormal prion protein can catalyze synuclein polymerization (Masliah et al., 2012). The relation of prion disease to aging is complex. Some prions such as those found in familial Creutzfeldt–Jacob disease (CJD) have very long latent periods of many decades while variant CJD derived from infected cattle progresses very rapidly (Avrahami and Gabizon, 2011).

While prion disease is infectious and self-propagating, it has led to the broader concept that Alzheimer's disease and other neurodegenerative states may arise from the misfolding and sustained corruption of endogenous proteins (Jucker and Walker, 2013). There is epidemiological evidence of an association between high levels of environmental manganese due to industrial pollution, and incidence of a variant of Jacob–Creutzfeldt disease with incomplete penetrance (Slivarichová et al., 2011). The prion protein associated with this disorder is normally a copper binding protein, and it has been proposed that excess manganese can displace such copper and promote the formation of a toxic beta-rich isoform (Brown, 2011). In an experimental animal model, Mn severely exacerbates toxic misfolding and alters aggregate solubility (Angeli et al., 2014). This is especially pertinent in view of the parallels between manganism and PD.

Metal ions can also catalyze the misfolding of amyloid-beta peptide, leading to the generation of indigestible protein aggregates (Matheou et al., 2015). Copper worsens both amyloid and tau pathology in a transgenic mouse model of AD (Kitazawa et al., 2009) and this may account for the reported association between levels of ingested copper and AD (Brewer, 2015).

1.4 Mediation of neurosenescence by other organ systems or endocrine factors

Exogenous factors can also influence brain aging by way of the endocrine system. Glucocorticoids are adrenal hormones secreted in response to stress and have valuable anti-inflammatory properties. This is a constructive and effective response but its evolutionary intent is as an acute reaction to a transient crisis. The prolonged presence of these hormones has a generally adverse effect. Extended glucocorticoid or corticotrophin administration releasing hormones exacerbate AD-like cognitive and neuropathological changes in experimental animals (Sotiropoulos et al., 2011; Filipcik et al., 2012; Joshi et al., 2012). The hippocampus is selectively vulnerable to such endocrine stress-related damage due to its high density of glucocorticoid receptors (Frodl and O'Keane, 2013). It is not difficult to imagine interactions between protracted exposure to chemicals such as solvents or airborne organic and metal particulates together with the chronic stressors common to human society being especially harmful to the aging brain. Such chemicals may be present in the workplace, or in the general environment, or in the home.

2 Recurrent factors in environmental promotion of neurodegeneration

2.1 Inflammation as a site of action of diverse environmental pollutants in the acceleration of aging

Heightened levels of inflammatory markers characterize the aging brain (Sharman et al., 2007; Bondy and Sharman, 2010). This takes place even in the absence of exogenous inflammatory stimuli and is thought to reflect the accumulation of responses to prior activation of the immune system. These reactive processes may be retained rather than dispersed subsequent to the insult (Qin et al., 2007). Such evidence of excess inflammatory activity is further exacerbated in the presence of several neurodegenerative conditions including Alzheimer's disease (Bondy, 2012). Increased cortical inflammation is apparent in experimental animals following exposure to various anthropogenic, globally pervasive chemicals that are suspected to promote neurodegeneration. These include aluminum and copper (Becaria et al., 2006), methyl mercury, manganese, and broadly used pesticides (Cambier et al., 2012; Sipos et al., 2012; Santos et al., 2013). There is evidence the elevated basal levels of inflammation can be associated with reduced responsivity to relevant exogenous stimuli such as bacterial infection (Sharman et al., 2002). Thus resistance to infection is likely to be reduced.

Particulate matter and gaseous air pollutants can produce mediators of inflammation capable of reaching the brain (Calderón-Garcidueñas et al., 2007, 2012). Diesel exhaust activates and primes microglia leading to neuroinflammation, and dopaminergic neurotoxicity (Levesque et al., 2011). Small nanoparticles derived from diesel exhaust particles reach the olfactory bulb by their nasal depositions. The combination of such effects with normal aging may lead to the early onset of Parkinsonism and other neurodegenerative diseases. Air pollution has been linked to neuroinflammation and neuropathology in young urban dwellers. Forty percent of children and young adults exposed to polluted urban air exhibit frontal tau hyperphosphorylation and 51% have amyloid-β diffuse plaques compared to 0% in low pollution controls. The appearance of pathology resembling that of early Alzheimer's and Parkinson's disease in urban children gives cause for concern (Calderón-Garcidueñas et al., 2013). In similarly exposed adults, elevated levels of inflammatory markers are correlated with greater cortical atrophy than that corresponding to the expected value for their age (Calderón-Garcidueñas et al., 2012). A very recent report of a study conducted over a 15-year period found a correlation between traffic-related air pollution and incidence of AD and vascular dementia (Oudin et al., 2015). While epidemiology cannot in itself demonstrate causality, together with findings from experimental animals, it is strongly suggestive.

Several broadly used pesticides such as the insecticide dithoate are also known to cause the immune system of nervous tissues to become overactive (Astiz et al., 2013).

Other common broad exposures result from recreational drug use. A range of disparate materials including, cigarette smoke, alcohol in beverages, and use of illicit drugs such as amphetamine have all been reported as provoking excess levels of brain inflammation (Kelly et al., 2012; Qin and Crews, 2012; Khanna et al., 2013). It is likely that these events are in part mediated throughout the body by systemic endocrine activation of stress related changes.

In conclusion, many agents formed as a consequence of human activity, pervade the world's air and water supply. Many of these, even if their primary impact appears to be on other organs, can produce inflammatory changes in the nervous system, which can then add to normal and corresponding changes ongoing in the aging organism. These modifications may all act in concert to over-activate immune responses in the CNS which is already undergoing gradual age-linked increases in intrinsic inflammation unrelated to exogenous provocation of the immune system. In this manner, environmentally prevalent xenobiotic agents can further foster processes that are already underway in the senescent brain. The immune system therefore, is a site of potential interactions between intrinsic aging processes and their aggravation by xenobiotic agents. Such amplification of senescence could involve simple additive events but may be synergistic and thus more potent than readily foreseeable.

2.2 Silent toxicity

Neurotoxic events can remain concealed for a prolonged period before neurological deficiencies become apparent.

2.2.1 Developmental damage

The consequences of embryonic exposure to an adverse agent may remain occult through most of the lifespan only to assert them at a much later time, as the organism enters senescence. This has been shown to be the case with lead treatment of the developing rat where, 20 months later, there is a much-delayed overexpression of the amyloid precursor protein (APP) and its amyloidogenic Aβ product (Zawia and Basha, 2005). Thus prenatal exposures may be relevant to the promotion of a

neurodegenerative disease confined to the elderly. A parallel case has been made for the hazard of prenatal exposure to the pesticide *N,N*-dimethyl-4,4′-bipyridinium dichloride (paraquat) as increasing risk of developing PD in later life (Zhou et al., 2011).

However, xenobiotic agents may also interfere with brain development, leaving a legacy of diminished redundancy not apparent until it is further compromised during aging (Weiss, 2000). This “silent damage” may not be evident for most of life but may become manifest only at a late stage of the lifespan when aging can unmask hidden shortcomings.

2.2.2 Disruption of resources until a critical threshold is attained

Exposure to environmental contaminants such as pesticides may accelerate decline of the dwindling dopaminergic capacities of the aging nervous system. The damaging effect of dopaminergic toxins is superimposed on the natural decline of dopaminergic neurons (Bäckman et al., 2006). Toxicants can overtly exert greater effects in the aging brain because the aging nervous system has already a diminished ability to withstand toxic challenges.

The “conformational disorders” discussed in the section on prion disease, involve gradual accretion of inadequately cleared protein complexes. These diseases may have an extended “silent’ phase” before the buildup of aggregated indigestible proteins has detectable consequences. The manifestation of clinical symptoms only appears when a critical toxic threshold is reached (Zerovnik, 2010).

A considerable length of time may elapse between exposure to an environmental toxicant and the onset of clear deficits. In all these situations, the long latency of such events makes the demonstration of causality difficult to uncover.

3 Conclusions

It remains to be determined whether metals and organic chemicals act by directly facilitating a specific neurological disease, or by promotion of overall aging, thereby widening the platform for the onset of neurodegenerative disease. The pressure toward elevated and irrelevant inflammation can be derived from routine age-related events and also from a range of chemicals and physiological processes (Fig. 1). The final common trajectory resulting from exposure to many apparently unrelated materials can be attributed to the onset of inflammation, which appears to be a standard response of the nervous system to diminished vigor. Thus any trend toward cellular fragility will be reflected in this characteristic but unsupportive reaction.

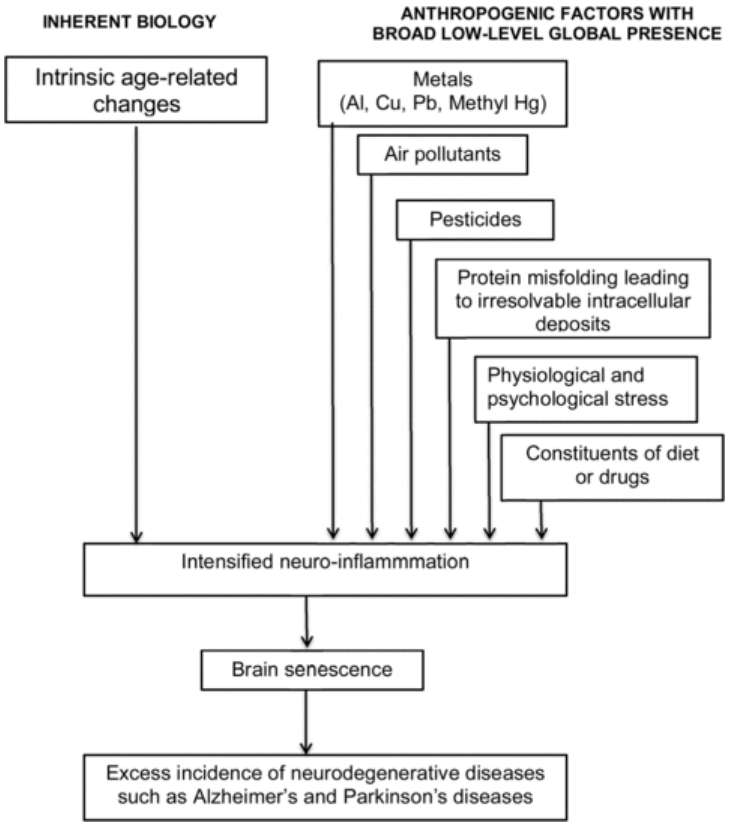

Fig. 1 Environmentally widespread factors and normal brain aging can each separately exacerbate inflammatory processes thereby leading to the excess incidence of neurodegenerative disease.

In the case of aluminum, it is possible that brain aging is generally accelerated by excessive levels of Al in drinking water, but this is not as readily detected as the relation between Al and the incidence of a specific disease such as AD (Bondy, 2012). Corresponding changes in frequency of less common brain disorders such as PD as a result of Al consumption are also harder to detect statistically.

The issue of lifetime cumulative exposure to low levels of various chemicals may be relevant to determining to rate at which brain aging occurs (Lucchini and Zimmerman, 2009). In view of the complexity of the exogenous factors that populations are exposed to, this is a difficult problem to address. It requires a painstaking examination of a range of both chemical and psychosocial factors followed by an evaluation of the potential for additive or synergistic interactions among them.

Conflict of interest

None.

Uncited reference

Bondy and Sharman (2007).

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