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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.

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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

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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