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The physiological and pathophysiological role of epinephrine and nor-epinephrine in Alzheimer's disease: a short communication

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Abstract

Alzheimer's disease (AD) is a progressive neuropathic disorder seen in older patients, resulting from a wide plethora of symptoms. Some of these symptoms include loss of cognitive and higher brain function at large. Clinical evidence points at the potential involvement of loss of adrenergic activity in the brain with this loss of cognitive function. Tests on rats and primates have shown that indeed there is a tight relationship between the Locus Ceruleus (LC) and the progression of AD. The LC being responsible for the production of two very important cathecolamines, epinephrine (EE) and norepinephrine (NE), both neurotransmitters involved in signal transmission. The immunological regulatory effects of NE loss have been shown to exacerbate the symptoms of AD due to impaired immunomodulation and immune-protection. Furthermore the age related effects of NE and EE have been shown in progressive loss of cognitive functioning which can be associated with AD.

Introduction

Alzheimer's disease (AD) is primarily categorized as a progressive neurodegenerative disorder having an unknown primary etiology, and is seen to usually affect individuals greater than 60 years of age **(Rossor 1993)**. It is clinically characterized by a uniform decline in cognitive functions particularly memory for temporally recent and distant events, attention, higher brain functions like reasoning and planning, language and judgment**(Auld 2002)**. There is no FDA approved cure for the disease and all parmaco-therapeutic treatments have been met with little or no clinical and symptomatic betterment**(Bartus 2000, Mann 2001)**. It has been seen that many pharmacological strategies have been employed to prevent or slow down the cognitive degeneration primarily using acetylcholinestrase inhibitors, whose mode of action is to increase the functioning and synaptic sensitivity of acetylcholine**(Bartus 2000, Auld 2002)**.

Epinephrine (EE) and epinephrine (NE)are cathecolamines which are active amines containing a catechol, and these act as neurotransmitters as well as hormones **(Sanchez et al., 2001)**. They control the autonomous as well as the central nervous system **(Benidect et al 1987)**. The sympatho-adrenal and hypothalamic-pituitary-adrenocortical axis (HPAA) interact to maintain the levels of NE and EE in the body. These two neurotransmitters are released in respose to adrenocorticotropic hormone which is in turn secreted in response to corticotropin releasing hormone/factor **(McCann et al., 2000)**.The synthesis of these neurotransmitters involves the biotransformation of L-Tyrosine into L-Dihydroxyphenylalanine by Tyrosine hydroxalase and O2 Tetrahydrobiopterin. L-Dihydroxyphenylalanine is then decarboxylated by Aromatic L-amino acid decarboxylase, into Dopamine. Dopamine is then hydroxylated by Dopamine β-hydroxylase in the prescense of O2 Ascorbic Acid into (4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol aka Norepinephrine. (4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol is then methylated by Phenylethanolamine*N*-methyltransferase along with *S*-adenosylmethionine into (R)-4-(1-hydroxy-2-(methylamino)ethyl)benzene-1,2-diol aka epinephrine **(Kvetansky et al., 1993)**. Finally there are five distinct adrenergic

receptors namely α (1 and 2), and β (1, 2 and 3), each which further can be divided into further subtypes, on which bothe NE and EE act **(Friedman et al., 1999)**.

The neuropathalogical representation of AD patients has shown intra-neuronal synaptic deterioration, deposition of extracellular beta-amyloid (Aβ) containing senile plaques along with the presence of neuro-fibrillary tangles which can be seen intracellularly**(Trojanowski et al, 1993)**. The mentioned findings are exhibited most prominently in the amygdala, hippocampus as well as the entorhinal cortex which is a constituent of the temporal lobe, association can be seen in in the frontal and parietal cortices, the lowest visualization of these neurodegenerative changes can be seen in the primary somatosensory, motor as well as motor cotices **(Medgett et al., 1978)**. Additionally an important pathological characterization is the progressive degeneration of noradrenergic nuclei in the brainstem primarily the locus ceruleus (LC), the LC being the major supply of NE and EE to the brain **(Heneka et al., 2010)**.

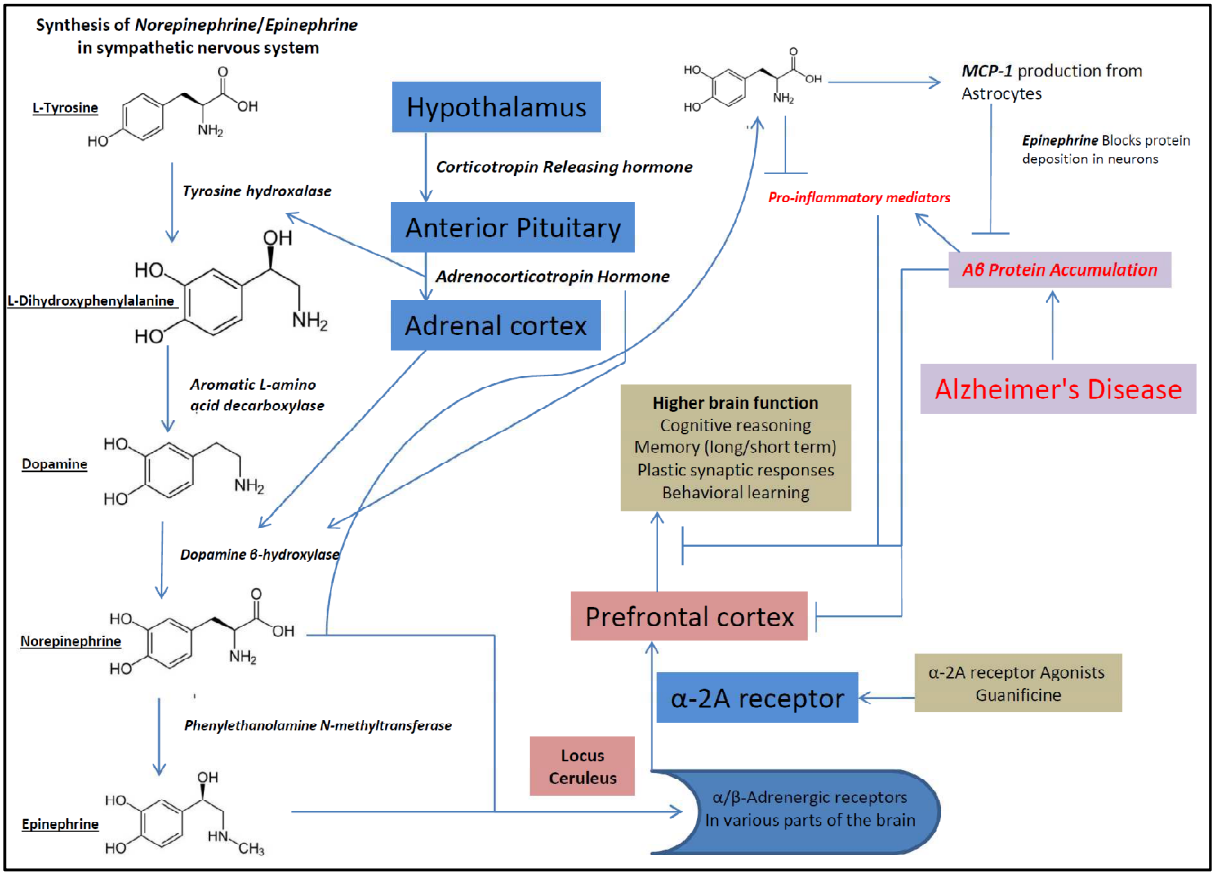

Figure 1. The active functional activation, of epinephrine precursor elements into epinephrine. Later epinephrine shows its activity on various adrenergic receptors in the Locus ceruleus and the prefrontal cortex.

Function of α-2 adrenergic receptors in cognition, loss resulting in Alzheimer's disease

NE acts at on five distinct adrenergic receptors namely α (1 and 2), and β (1, 2 and 3), each which further can be divided into further subtypes **(Friedman et al., 1999)**. Post junctional stimulation of α-2 receptors in the principal sulcus result in the beneficial neurotransmitive properties of NE particularly cognitive reasoning **(Goldman-Rakic et al., 1990)**. Controlled drug mediated pre frontal cortex degradation can result in spatial lag and loss of higher cognitive reasoning in primates, these symptoms have been shown to be reverted using exogenous α-2 agonists like clonidine **(Arnsten and Goldman-Rakic 1985)**. Other experiments show the enhanced cognitive ability in non-human primates using guanfacine a potent α-2 receptor agonist **(Arnstenet al., 1988; Schwartz et al., 2000)**. Differential studies using positional cloning has identified three receptor subtypes in human α-2A, α-2B and α-2C **(Kobiha et al., 1987; Lomasney et al., 1990; Regan et al., 1988)**. Alpha-2A and α-2C have been shown to be primarily resident in the thalamus, relating to the adverse effects or NE and EE **(Reis et al., 1984).** It is interesting to note however that the α-2A subtype has been isolated to be present in the pre frontal cortex, certifying the selective activity of guanfacine**(Aoki et al., 1994)**. Nevertheless it is pertinent to mention that α-2 receptor activation by NE is associated with better cognitive function, α-1 receptor modulation results in impaired frontal cortex related cognition **(Uhlen et al., 1995)**.

Function of β-2 adrenergic receptors in cognition, loss resulting in Alzheimer's disease

The basolateral amygdala induces hippocampal long term potentiation implicated in learning as well as memory; this is mediated by the activity of β-adrenergic receptors present in the amygdala **(Ikegaya et al., 1996)**. Infusion of β-adrenergic antagonists induces loss of cognitive ability **(Ikegaya et al., 1997)**,

whereas the administration of β-adrenergic agonists reverses cognitive and memory deficits produced due to NE deficits in animal models **(Crowe and Shaw 1997)**. Interestingly neuroscientists have shown that emotional arousal mediated memory conjunction is related to β-adrenergic receptor function, as administering a β-adrenergic antagonist resulted in loss of this ability in test subjects **(Cahill et al., 1994; Van Stegeren et al., 1998)**.

The role of the Locus Ceruleus in Alzhiemer's disease

Research on the involvement of LC degeneration in the pathogenesis of AD has been studied by many scientific groups since the 1960s **(Forno 1966; Iversen et al., 1983; Bondeareff et al., 1987)**. A study of particular has shown that AD patients have a exhibited loss of LC neuronal cells, reducing to as low as 70% in the rostral nuclei leading to reduced limbic and cortical NE levels **(Matthews et al., 2002)**. This drop in levels of NE has shown strong co-relation with the extent of cognitive and memory dysfunction in AD patients **(Heneka et al., 2010)**. A study shows 80% patients suffering from mild cognitive impairment eventually result in AD **(Petersen et al., 1992)**. Hence there is an association of loss of cognitive function with AD further certifying the aforementioned **(Gurdzien et al., 2007)**. Degeneration of LC neurons, have been shown to result in the progressive loss of either conventional synaptic contacts or varicosities. Varicosities have been shown to release norepinephrine extracellularly resulting in modulation of surrounding neurons, blood vessels and glial cells **(Marien et al., 2004)**.

Norepinephrine and Epinephrine as anti-inflammatory agents in the brain

Norepinephrine (NE) and epinephrine (EE) has a contribution towards consolidation, acquisition and retention of information during normal neuro-physiological conditions **(Murchison et al., 2004)**. NE has also shown to have strong anti-inflammatory properties especially during several pathological instances **(Feinstein et al.,**

2002). There is strong reference in literature to the negative influence of norepinephrine on the regulation of transcription of inflammatory genes in astrocytes and microglial cells **(Feinstein et al., 2002).** It is notable that both cells possess functional adrenergic receptors **(Mori et al., 2002)**. Further studies have shown that this effect is indeed mediated by β2-adrenergic receptors, hence proposing the endogenous anti-inflammatory potential of NE and EE, alleviating the risk of AD**(Mori et al., 2002)**.

Loss of immune-protective Norepinephrine results in the presentation of Alzheimer's disease

In an experiment where an animal model was generated for AD having LC degeneration using an APP-transgenic mouse **(Heneka et al., 2006)**. It was shown that use of norepinephrine in these mice, abolished the increased gene transcription of pro-inflammatory cytokines TNFα, CCL2, iNOS and COX2 **(Heneka et al., 2010)**. There is a strong relationship between the deposition of neurodegenerative protein Aβ and increased presence of inflammatory mediators in the brain **(Förstl et al., 1994)**. Hence the increased activity of the innate immune system in response to Aβ will lead to increased neuro-degeneration implicated in AD. NE is immunoprotective in this aspect by reducing Aβ deposition as well increasing the secretion of neuroprotective chemokines like MCP-1 from astrocytes **(Madrigalet al., 2007).** MCP-1 in turn protects neurons from Aβ-mediated damage involving PPARδ and GSH-synthesis **(Madrigal et al., 2009)**. Arguably NE and EE serve as immune-protective immunobiological responses by the host, however tight regulation of cytokines and other inflammatory mediators is imperative in the prevention of neuronal damage by microglial cell populations **(Henaka et al., 2010)**.

The effect of age on norepinephrine concentrations

There is an increased incidence of age related loss of noradrenergic functioning which can be related to a factor associated with increased risk of AD **(Ramirez et al.,**

2004). This has been seen in some studies the stimulation of the LC will result in alleviation of memory deficit, using certain LC stimulating agents like α-2 receptor antagonist piperoxane**(Froc et al., 2003)**.

Conclusion and avenues for future study

It can be seen that the age related deficiency of adrenergic activity in the pre frontal cortex due to decreases LC functioning as well as decreased immune-protective function results in the higher of AD. In case of AD patients absence thereof, further potentiates the symptoms of AD due to no protective function being rendered by the brain to protect normal un affected neurons. This cascade of effects leads to the pronounced presentation of AD symptoms. The strong association with norepinephrine has already been established in data, however further insight is required in case of epinephrine, and its involvement in long term memory in relation to AD. Some clinics in the USA are already using adrenaline as a therapeutic option in case of AD, but it is also established that epinephrine does not easily cross the blood brain barrier so the efficacy of this treatment needs to be validated. The molecular basis for LC regulation and adrenergic innervation of the pre-frontal cortex needs to be ameliorated with data, and further evidence is required to stratify mechanisms involved in Aβ deposition in neuronal cells of different regions in the brain. Use of adrenergic agonists in combination with cholinergic drugs may increase cognitive function and delay the adverse cognitive degeneracy effects associated with progressive geriatric AD. There is also the need to correlate the presence of strong clinical evidence that points towards β-adrenoreceptor involvement in elevated cerebrospinal EE and NE levels in progressive AD patients, is this a physiological compensatory response to reduced NE in the brain, or does AD pathology adversely affect sympathetic functioning.

Conflict of interest:

The authors state they have no conflict of interest with any other scientist or institution.

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