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Nitric Oxide: The Common Link in Different Forms of Dementia

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ABSTRACT

Dementia broadly refers to a global decline in cognitive and higher functions of the brain. With the gradually increasing number of aging population, the incidence of dementia has been steadily rising and expected to increase further in the coming years. The causes and forms of dementia are wide-ranging and diverse, with Alzheimer's disease being its best studied form. With increasing knowledge about various effects and mechanisms of nitric oxide, this chemical neurotransmitter appears to be the connecting link in the cellular pathogenesis of dementia. An exhaustive search of research articles, commentaries and books published from 1990s onwards was performed with various words and combinations linked to dementia and nitric oxide. The existing medical literature shows both neuroprotective and neurotoxic effects of nitric oxide. The present article intends to delve into this topic and provide a lucid understanding of the role of nitric oxide in dementia.

Key words: Dementia, Nitric Oxide, Alzheimer's disease, excitotoxicity, nitrosative stress

INTRODUCTION

Expansion and improvement in the intellectual and analytical abilities have been at the epicentre of our journey through the process of evolution. The human brain is highly specialized in a vast array of higher cognitive, behavioural and executive functions. The term dementia broadly refers to a global decline in these functions. The International Classification of Mental Disorders (ICD 10)[1] defines dementia as a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning, language and judgment. It is a neurodegenerative disorder, generally characterized by a progressive loss of synapses and neurons.[2] Etiologically, the various forms of dementia are primary degenerative disorders, vascular dementias and those secondary to infections, metabolic, nutritional and toxic causes.[3] The primary forms include Alzheimer's disease, Fronto-temporal degenerations, Lewy Body dementia, Huntington's disease; etc and vascular dementias occur consequent to infarctions of the brain. Alzheimer's disease (AD) is the most common and perhaps the best studied form of dementia which is estimated to affect nearly 36 million people worldwide. Dementia is largely a disease affecting the elderly people, especially above 60 years of age. It is estimated that both the prevalence and incidence of dementia nearly doubles every 5 years in the population above 65 years, reaching a prevalence of as high as 35% in those above 85 years.[3] Over the years, as the health-care facilities have improved by leaps and bounds, the number of aging population has also increased steadily. And therefore, the occurrence of dementia is set to increase further in the coming years. Estimates provided by the WHO project that about 75% of the people aged 60 years and older will reside in

developing countries by 2025.[4] Consequently, the highest rates of growth in cases of dementia (about 336%) are expected to be in the developing countries like India, China, South Asia, and western Pacific regions.[5] With regard to the Indian scenario, studies conducted across various regions have revealed the prevalence rate of dementia to be ranging from 0.8% to 4.1%. [6]

Alzheimer's disease

The two defining pathological features of Alzheimer's disease, the commonest form of dementia are extracellular amyloid plaques and intracellular tangles composed primarily of amyloid β (Aβ) peptide and hyperphosphorylated form of tau protein.[3] Genetic mutations involving commonly the presenilin-1 or presenilin-2 genes are responsible only for the familial variant of the disease, the incidence of which is very rare.[7,8] Majority of the cases are sporadic or late-onset and their precise etiology is currently unknown.[9]

Nitric Oxide: The common factor

Interestingly, cardiovascular risk factors like hypertension, hypercholesterolemia, diabetes mellitus, aging, and sedentary lifestyle are associated with higher incidence of this form of dementia. Though the exact connecting link between these factors remain to be unveiled, one common feature among all of these is endothelial dysfunction, specifically, decreased bioavailability of nitric oxide (NO).[10,11] It is thus prudent to assume that Nitric Oxide has a significant role to play in the pathogenesis as well as the long-term outcomes in cases of dementia.

What is Nitric Oxide?

Nitric Oxide was initially identified as a compound released from the endothelium of blood vessels responsible for causing vasodilation. It was later also identified as a chemical neurotransmitter in the brain. It is produced from the amino-acid L-arginine through a reaction that is catalysed by the enzyme Nitric Oxide synthase (NOS).[12,13] There are three different isoforms of this enzyme, encoded by three different genes: NOS1, NOS2 and NOS3, that encode the neuronal, inducible, and endothelial NO synthases (nNOS, iNOS, and eNOS), respectively.[12-14] Among them, NOS1 is primarily localized to nervous tissue, NOS2 in activated macrophages and NOS3 in the endothelium. At the cellular level, there are three possible nitric oxide signalling pathways. They are soluble guanylate cyclase and the cyclic guanosine monophosphate (cGMP) pathway [15], direct S-nitrosylation of protein cysteine residues[16] and protein tyrosine nitration. [17]

There are certain unique features of nitric oxide in context of its function as a neurotransmitter. It exists in gaseous state and therefore can freely diffuse across membranes. Thus it is a powerful signalling molecule with far-reaching cellular consequences. The present corpus of research literature suggests that Nitric oxide can be both beneficial and detrimental, i.e. it can be neuroprotective and maladaptive depending on the neuronal environment, source of secretion and coexistence of other inflammatory events.[14] By itself, it is also a very reactive chemical and has an extremely short half-life (less than 5 seconds).[13] It is not stored in vesicles in the pre-synaptic membrane like most other classical neurotransmitters.[12] Rather it is synthesized from post-synaptic sites whenever there is demand or a suitable stimulus like activation of NMDA receptors and subsequent Calcium influx in cells of the hippocampus, which is a pivotal structure in the brain concerned with learning and memory consolidation. Its gaseous state allows it to affect the neuronal processing and synaptic functions in the adjoining areas also. Nitric oxide has multiple physiological aspects of action. It acts as a vasodilator, inflammatory mediator and also a neuromodulator which can therefore bear varied effects on the brain. It influences vascular homeostasis by promoting vasodilatation, inhibiting platelet aggregation and leukocyte adhesion. Nitric

oxide also decreases LDL oxidation by inhibiting NADPH reductase activity resulting in a strong anti-atherogenic effect. [13] Also, at high concentrations, it reacts with the free-radical, superoxide anion that is formed as a by-product of respiration, to generate peroxynitrite, which is a highly reactive oxidant and cytotoxic molecule.[18]

The plausible role of Nitric Oxide in decline of higher functions in dementia

Long-term studies on dementia and especially its classical form, Alzheimer's disease put forward data which suggest that the disease pathogenesis commences decades before apparent cognitive decline. [19,20] Additionally, a clinical entity called Mild cognitive impairment (MCI) is also recognized which denotes the transitional phase between normal aging and dementia. The physiological derangements starting in this phase mostly progress to dementia. The community prevalence of Mild cognitive impairment in India is about 14.89%. [6]

a. Oxidative and nitrosative stress

Two mechanisms have been proposed that start occuring before the classical hallmarks of dementia and Alzheimer's disease develop. They are oxidative and nitrosative stress: the result of increased levels of reactive oxygen and nitrogen species, respectively. They have been reported to be found in brains of these patients before the accumulation of Aβ and phosphorylated tau.[21,22] Oxidative stress is proposed to be mediated by the peroxynitrite molecule. The role of nitric oxide in its genesis has been mentioned in the preceding section. Nitrosative stress in the cerebral cortex is proposed to be mediated by a process called excitotoxicity. One of the commonest chemicals which cause excitotoxicity is glutamate. Nitric oxide plays an important role in the genesis of glutamate in brain areas specific to learning and memory as discussed in the next section. Glutamate is normally cleared from the brain's extracellular fluid by Sodium-dependent uptake systems maintaining a proper-gradient between the inside of a neuron (millimolar levels) and the ECF of the brain (micromolar levels). [12] Glutamate behaves much like a double-edged sword. While being required for neuronal signalling it also poses the risk of cellular death because glutamate can produce calcium influx to such an extent that the cell body of the neuron dies. This is one of the important mechanisms now recognized to cause dementia after cerebrovascular events like stroke. The area surrounding the cerebral infarct although survives loses its ability to maintain sodium-gradient which consequently leads to accumulation of glutamate and excitotoxic neuronal death.[12]

b. The role of NMDA receptors

Physiologically, one of the important cellular mechanisms of encoding of memory and learning is long-term potentiation (LTP). It involves repetitive stimulation of NMDA receptors and enhancing synaptic plasticity in neurons. However, prolonged, high intensity activation of extra-synaptic NMDA receptors triggers cell death pathways.[23,24] In addition to this, in the cells of the hippocampus, neuronal NOS is found to be co-localized with NMDA receptors in the postsynaptic membrane and after Ca^{2+} influx into postsynaptic neurons, NO acts as a retrograde messenger providing a positive feedback mechanism to maintain or increase glutamate release from the pre-synaptic terminal which then act on the NMDA receptors.[25] Importantly, NO also causes a reduction in the NMDA receptors, especially in the cortex and hippocampus.[14] Triggering of apoptotic pathways in neurons and excitotoxic effect subsequent to LTP can eventually cause a decline in the cognitive functions. On the other hand, reduced number of NMDA receptors can by itself impede the process of memory and learning. This explains how low as well as high levels of nitric oxide have the potential of behaving both in a beneficial and a maladaptive way. An adverse effect would cause cognitive decline and lead to dementia. Decreased levels of the enzyme nitric oxide synthase

(NOS) in patients of dementia and Alzheimer's disease have been reported by Norris et al[26] and Gargiulo et al.[27] Increased expression of the same has been found by Dorheim et al[28] and L¨ uth et al.[29] It can be well deduced that an increase or decrease in the enzyme expression would directly affect the levels of the molecule, nitric oxide. Decreased levels of serum nitric oxide (NO) have been observed by Corzo L et al [30] and Selly ML [31] in different forms of dementia and also in cases of probable Alzheimer's disease.

c. Vascular effects

Low levels of nitric oxide in blood would lead to vascular dysfunction because nitric oxide has vasodilator and atheroprotective effects.[32] This could also lead to dementia.[33]

CONCLUSION

The currently known physiological mechanisms of Nitric Oxide provide reasonable teleological ground to believe that both reduced and elevated levels of the molecule can affect synaptic processing in brain centres crucial to higher functions like the hippocampus and cortex. There are epidemiological evidences in favour of both. However, those in favour of reduced nitric oxide being associated with dementia appear to be slightly more, especially if we consider its effect on vascular smooth muscle and anti-atherosclerotic effect. Given its beneficial as well as detrimental effects, a unanimous consensus on the exact role of nitric oxide in the pathogenesis is yet to emerge, but it can be definitely concluded that nitric oxide is a vital connecting link between the different types of dementia.

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