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EDITORIAL

WHAT IS THE PHYSIOLOGICAL FUNCTION OF AMYLOID-BETA PROTEIN?

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Most of the studies of amyloid-beta (Aβ) have concentrated on the pathological effects of high levels of the protein in causing cognitive impairment and Alzheimer's disease (1). There is some evidence that the Amyloid Precursor Protein (APP) has a physiological trophic function on the central nervous system (2). APP knockout mice are viable but have smaller brains and alterations in neurogenesis (3). APP plays a role in the nervous system, possibly through promotion of neurite outgrowth and also long-term potentiation (LTP) by modulation of calcium release (4, 5).

In neuronal cultures, inhibition of Aβ production by blocking beta-secretase leads to neuronal cell death, and this can be prevented by providing physiological doses of Aβ (in the picomolar range) (6). Aβ at physiological levels reduces the excitatory activity of potassium channels and reduces neuronal apoptosis (7). Soucek et al (8) have suggested that a physiological effect of Aβ during aging is neuroprotection, secondary to its ability to induce hypoxia inducible factor-1α.

Other suggested physiological effects of Aβ include antimicrobial activity, blocking leaks in the blood-brain-barrier, enhancing recovery from posttraumatic brain injury and possibly suppressing cancer through inhibition of oncogenic viruses (9).

Aβ at picomolar concentrations enhances synaptic plasticity and learning and memory in animals by promoting LTP in the hippocampus. Its action involves increasing the release of the neurotransmitter acetylcholine and activation of nicotinic acetylcholine receptors (10-12). However, it is important to note that prolonged exposure is associated with tolerance leading to reduced effects of Aβ.

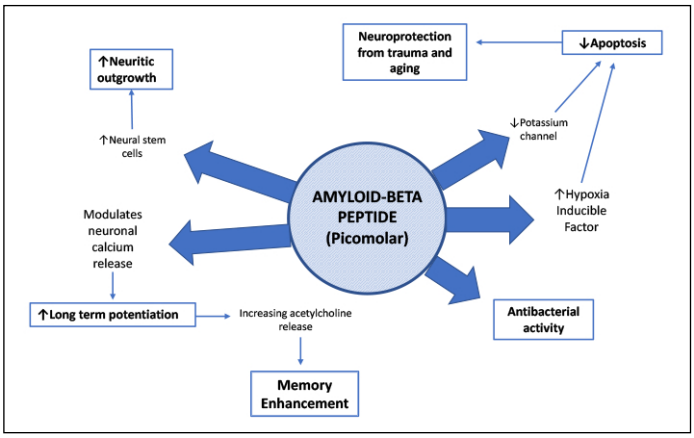
Ours and many other studies on neurotransmitter roles in memory have demonstrated that while low (physiological) doses enhance memory, high (pathological) doses inhibit memory (13-15). This phenomenon is known as hormesis (16). Specifically, our group had shown that high doses of Aβ inhibited memory in mice (17), while low dose (picomolar) quantities of Aβ enhanced memory in mice (10). This has been consistent with results demonstrated by others (11, 12). We further showed that the converse was true, as both antibodies to Aβ and antisense to APP mRNA resulted in impaired memory in young mice (17).

The physiological role of Aβ explains why when drugs that reduce Aβ are used to treat Alzheimer's disease they fail (18-20). This is due to these drugs eventually reducing the Aβ to values where they interfere with the physiological activities of Aβ.

In an attempt to reduce Aβ to normal levels but be able to modulate the treatment to prevent lowering levels below normal, we have developed a series of antisense to APP (21, 22). These antisenses reduce Aβ to the normal range, improve memory, decrease oxidative damage and improve blood-brain-barrier function in mouse models of Alzheimer's disease (23-27). These antisenses can be administered intranasally. We believe that antisenses such as these may well have a therapeutic role in the management of Alzheimer's disease in humans.

In conclusion, this editorial argues that the physiological role of Aβ is to improve memory (Figure 1), and it is only when Aβ levels are markedly increased that they result in dementia as predicted by the "Amyloid Hypothesis."

Figure 1
The physiological role of amyloid-beta peptide



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