Research Focus

Living with the enemy: a physiological role for the β-amyloid peptide

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The Aβ peptide, which is derived from the processing of the amyloid precursor protein APP, is the principal agent responsible for the pathogenesis of Alzheimer's disease. In a recent study by Kamenetz *et al.*, Aβ is shown to mediate a physiological homeostatic mechanism that reduces excitatory transmission in response to neuronal activity. Failure of this autoregulatory feedback could lead to the neuropathology of Alzheimer's disease.

Alzheimer's disease is the most common form of senile dementia, affecting 10% of individuals >65 years of age and nearly half of those >85. The pathophysiology of this illness has been associated with a variety of factors, including the deposition of β-amyloid plaques, accumulation of intracellular neurofibrillary tangles, oxidative neuronal damage and inflammatory cascades [1]. However, it is now widely believed that an increase in the production of the β-amyloid peptide (Aβ, the main component of the β amyloid plaques) is central to the pathogenesis of Alzheimer's disease [2–4]. Since the first description of the neurotoxic properties of the Aβ peptide [5], an enormous number of studies have investigated the cellular and molecular pathology triggered by Aβ. Nevertheless, it is still far from clear how the accumulation of this peptide leads to the cognitive decline that is characteristic of Alzheimer's disease patients. More importantly, it has remained uncertain whether Aβ had any normal physiological role in the brain. This picture could change after a recent report by Kamenetz, Malinow and colleagues [6]. By using an elegant combination of genetics, pharmacology and electrophysiology on brain tissue, these authors have described a physiological role for Aβ in modulating neuronal activity. Furthermore, they propose a model for the neuronal dysfunction that accompanies the excessive production of Aβ.

A homeostatic role for Aβ in modulation of neuronal activity

The Aβ peptide is formed upon proteolytic processing of the amyloid precursor protein (APP) by β- and γ-secretases. Unprocessed, full-length APP has been proposed to have a role in axonal transport of membrane-associated cargo [7]. In addition, the intracellular C-terminal fragment that results from APP processing by γ-secretase functions in gene expression as a transcription factor [8,9]. By contrast, the Aβ peptide was commonly considered as a dangerous, unfortunate byproduct of APP processing, despite the fact that Aβ is present in the cerebrospinal fluid and plasma of healthy individuals throughout life [10]. It had been previously proposed that Aβ might act as a physiological regulator of ion channel function in neurons, based on studies using exogenously added Aβ peptides and neuronal primary cultures [11,12]. However, it remained to be proven whether endogenous Aβ secreted by neurons had any physiological role in the brain. Perhaps the most important contribution of the work by Kamenetz *et al*. [6] to the Alzheimer's disease research field are the observations that Aβ is secreted from healthy neurons in response to activity and that Aβ, in turn, downregulates excitatory synaptic transmission. This negative feedback loop, in which neuronal activity promotes Aβ production and Aβ decreases synaptic activity, would provide a physiological homeostatic mechanism to maintain the levels of neuronal activity in check (Figure 1). This article describes the implications of this link between Aβ production and synaptic transmission.

Neuronal activity promotes Aβ formation

It had been previously reported that neuronal depolarization [13], as well as a variety of neurotransmitters, growth factors and hormone receptors [14], modulate the generation of APP secretory products. Nevertheless, neither the mechanisms involved nor the functional relevance of this regulation was clear. The study by

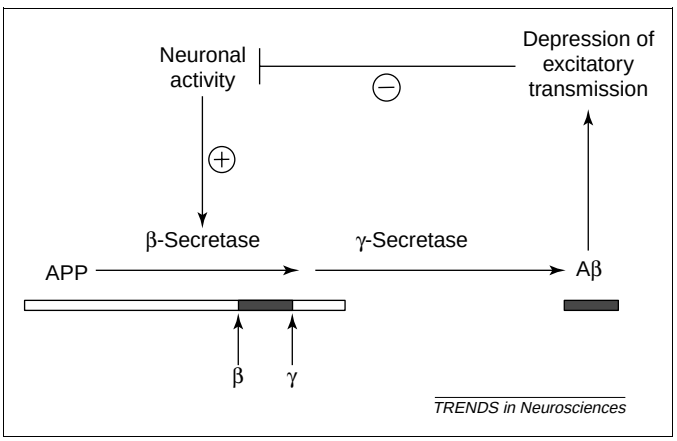

Figure 1. Model for homeostatic control of neuronal activity by the β-amyloid peptide, Aβ. Aβ is formed from amyloid precursor protein (APP) by the action of β- and γ-secretases. Neuronal activity increases β-secretase function, leading to enhanced secretion of Aβ. Aβ, in turn, depresses excitatory transmission, which will result in a reduction of neuronal activity. The regulatory feedback loop between neuronal activity and Aβ production is broken in Alzheimer's disease patients, resulting in unchecked accumulation of Aβ and neurotoxicity.

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Kamenetz *et al*. now reveals that spontaneous neuronal activity enhances the β-secretase-mediated cleavage of APP, leading to an enhanced secretion of the Aβ peptide. The regulatory effect of Aβ requires NMDA receptor activation. Therefore, it seems reasonable to speculate that NMDA receptor opening, with the concomitant entry of Ca^{2+} into the postsynaptic terminal, triggers the signaling cascade that results in enhanced β-secretase activity. However, the molecular details that mediate this regulatory cascade remain to be elucidated.

Importantly, neuronal activity was shown to regulate both the low-level basal secretion of endogenous Aβ and the enhanced secretion produced by the Swedish mutation of APP (this mutation is linked to some forms of familial Alzheimer's disease and has been shown to increase production of Aβ). These results have potential therapeutic relevance because they indicate that production of Aβ can be slowed by reducing neuronal activity. Interestingly, two recent clinical studies support this interpretation: benzodiazepines, which enhance inhibitory transmission (thus reducing excitatory drive), and memantine, an NMDA receptor antagonist, protected against cognitive decline in Alzheimer's disease patients [15,16].

Aβ secretion downregulates excitatory synaptic transmission and plasticity

There have been numerous studies on the effect of Aβ on neuronal function. These investigations usually involved the addition of exogenous Aβ peptides to neuronal preparations, with the concomitant uncertainties concerning peptide aggregation state and access to subcellular compartments. Alternatively, animal models expressing mutated proteins associated with familial Alzheimer's disease have been very valuable for behavioral and physiological studies. However, these models are often subject to potential developmental alterations. Kamenetz and colleagues have taken advantage of an organotypic slice culture system from hippocampus, which combines the versatility of *in vitro* preparations with the physiological power of a semi-intact system. This allowed them to express wild-type APP or different APP derivatives acutely under several pharmacological situations and study the effects of endogenously produced Aβ on synaptic function and plasticity. The central conclusion of this extensive series of experiments is that the Aβ depresses fast excitatory synaptic transmission (mediated by AMPA and NMDA receptors) but not inhibitory transmission (mediated by GABA receptors). This effect is exerted by removing functional synapses, because electrophysiological parameters that reflect separately presynaptic or postsynaptic function were not affected by enhanced Aβ production. In agreement with previous studies using exogenously added peptides, Kamenetz *et al*. showed that Aβ acts in a non-cell-autonomous manner – that is, it affects both the neuron producing Aβ and its neighboring cells. Although the mechanisms by which Aβ leads to synaptic removal remain unknown, it is worth noting that soluble, non-aggregated Aβ enhances Ca^{2+} [12,17] and K^{+} [11] channel activity, which could result in altered synaptic function.

The study by Kamenetz *et al*. also showed that Aβ production impairs long-term potentiation (LTP), a paradigmatic form of synaptic plasticity that is widely accepted as a cellular correlate for learning and memory. Obviously, these results are very important for understanding the cognitive decline and memory deficits associated with Alzheimer's disease. Interestingly, the effects of Aβ on synaptic transmission and plasticity were apparent at levels of Aβ production well below those necessary for plaque formation. These results reinforce the growing opinion that the initial stages of cognitive decline in Alzheimer's disease patients could be due to early disruptions of synaptic function mediated by Aβ before plaque formation or neuronal cell death [18]. It is also important to mention that the effects of Aβ on synaptic function were reversible. This result offers hope for therapeutic interventions designed to slow down or block the production of Aβ, because these might revert early pathological stages of the disease.

Concluding remarks and unresolved questions

The proposal of a physiological role for Aβ has been supported by a very recent report showing that production of Aβ is important for neuronal viability in primary cultures [19]. Still, this interpretation is not free from controversy. For instance, the knockout of the Aβ precursor, APP, causes only minor neurological defects [20], although it presents enhanced sensitivity to kainate-induced seizures [21]. Also, mouse knockouts of the primary β-secretase, β-site APP-cleaving enzyme 1 (BACE1), have no detectable behavioral or neurological deficits, despite the fact that production of Aβ in these animals is virtually abolished [22,23]. In this sense, it should be kept in mind that rodent brain contains very low levels of endogenous Aβ, and rodent Aβ is considered to be non-amyloidogenic [24]. Obviously, these are important issues when evaluating the physiological relevance of studies involving the overexpression of human Aβ in rats or mice. However, in support of a physiological role for Aβ in neurons, Kamenetz *et al*. showed that pharmacological blockade of endogenous rodent Aβ production leads to enhanced spontaneous neuronal activity and synaptic plasticity [6]. This issue is likely to stir further investigations.

The work by Kamenetz and colleagues has provided a solid framework for the elucidation of the mechanisms by which Aβ impairs synaptic transmission. Further studies can now concentrate on understanding how Aβ leads to the removal of excitatory synaptic connections. In addition, it will be important to identify the signaling cascade that leads to the enhanced processing of APP upon opening of NMDA receptors. Obviously, the central question that remains unanswered is why the regulatory feedback loop between neuronal activity and Aβ production is broken in Alzheimer's disease patients, resulting in unchecked accumulation of Aβ and neurotoxicity. Kamenetz *et al*. propose two possible scenarios. On the one hand, neurons might fail to be depressed by Aβ, leading to a gradual build-up of neuronal activity and further Aβ secretion. On the other hand, the machinery for Aβ production might become constitutive – that is, independent from neuronal activity. It is possible that different causes will underlie the

different forms of familial Alzheimer's disease and the more prevalent sporadic form of this illness. Future studies will hopefully clarify these issues.

Although multiple mechanistic questions remain open, the study by Kamenetz and colleagues has furthered our understanding of the pathological processes leading to Alzheimer's disease. But perhaps more importantly, this work has challenged our traditional perception of the β-amyloid peptide. Originally thought of as a toxic waste product, it is now been revealed as an endogenous regulator of neuronal activity. We can only hope that this new knowledge will help us to design better therapeutic strategies for when the time comes to fight the enemy within.

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