Review Article

Amyloid Beta-Protein and Neural Network Dysfunction

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Understanding the neural mechanisms underlying brain dysfunction induced by amyloid beta-protein (Aβ) represents one of the major challenges for Alzheimer’s disease (AD) research. The most evident symptom of AD is a severe decline in cognition. Cognitive processes, as any other brain function, arise from the activity of specific cell assemblies of interconnected neurons that generate neural network dynamics based on their intrinsic and synaptic properties. Thus, the origin of Aβ-induced cognitive dysfunction, and possibly AD-related cognitive decline, must be found in specific alterations in properties of these cells and their consequences in neural network dynamics. The well-known relationship between AD and alterations in the activity of several neural networks is reflected in the slowing of the electroencephalographic (EEG) activity. Some features of the EEG slowing observed in AD, such as the diminished generation of different network oscillations, can be induced in vivo and in vitro upon Aβ application or by Aβ overproduction in transgenic models. This experimental approach offers the possibility to study the mechanisms involved in cognitive dysfunction produced by Aβ. This type of research may yield not only basic knowledge of neural network dysfunction associated with AD, but also novel options to treat this modern epidemic.

1. Introduction

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by severe cognitive impairments [1, 2]. Postmortem studies of brains from long-term AD patients have revealed the presence of senile plaques that contain the amyloid beta-peptide (Aβ) [3, 4]. Most studies of AD have focused on the biochemical mechanisms involved in the neurodegenerative processes triggered by the Aβ aggregates (for recent reviews, see [5, 6]). Such efforts have provided noteworthy evidence that has explained some aspects of the disease, mainly in its terminal stages; however, it has been difficult to link these findings to the known cognitive and behavioral symptoms that characterize the early stages of the disease. Moreover, new therapeutic approaches to treat AD based on this research have shown little or no benefit (for a recent review, see [7]). By looking at the cellular mechanisms involved in AD physiopathology from another perspective, it is becoming clear that cognitive decline associated with AD, or with any other neurological disease, should be examined in the context of the related neural network dysfunctions [1, 2, 8–10]. This approach, which might look novel for AD, has had proven success for the understanding of other neurological diseases (e.g., epilepsy; for a recent review, see [11]). One of the main findings supporting this approach in AD is the observation that long before massive neural loss is observed in these patients, there is a significant, early decrease in neuronal activity in various circuits throughout the brain [12, 13], which has also been observed recently in a transgenic mouse model that develops an AD-like pathology [14]. Thus, leaving neurodegeneration aside, we must consider that cognition requires the activity of neural networks (Figure 1) and that knowing how neural network activity is altered in AD will provide a basis to understand the cellular mechanisms of this disease and will allow us to explore new therapeutic avenues against this disease [8–10, 15] (Figure 1).

Over the last several years, evidence has indicated that Aβ is the causal factor for the early cognitive decline observed in AD [1, 2, 8, 9]. Evidence supporting this relationship includes the close correlation between the level of soluble oligomeric forms of Aβ and the cognitive decline in AD
patients [3, 4]. Moreover, it has been demonstrated that Aβ acutely disrupts learning and memory after infusion into the CNS [16–19] and that this Aβ-induced cognitive dysfunction can be maintained for long periods of time [20–22]. But, what is the origin of Aβ-induced cognitive dysfunction?

As mentioned, cognition arises from the activity of specific cell assemblies of interconnected neurons that generate neural network dynamics expressed in various patterns of population activity [23–25] (Figure 1). The cellular mechanisms involved in the generation of the different patterns of activity, as well as their specific generators, have been extensively studied in the last decades (for extensive review on this issue look at [23–25]). Of course, these patterns of network activity can be modulated by the intrinsic and synaptic properties of the neurons involved in the circuits in a state-dependent manner (i.e., rest versus active processing; [26]) (Figure 1). Thus, the origin of Aβ-induced cognitive dysfunction must be found in specific alterations in these properties and their consequences in neural network dynamics, as has been explored recently [27–36] (Figure 1).

Several patterns of neural network activities have been linked to specific cognitive processes (Figure 1). For instance, a strong correlation between memory formation and theta rhythm generation has been consistently demonstrated in rodents [24] and humans [40] (Figure 1). Similarly, gamma rhythms have been associated with several cognitive processes [37]. Supporting this association, recent experiments have shown that enhancing gamma activity by optogenetic means increased performance of circuit processing and improved cognition [41], which indicates that the modulation of neural network activity could be used to treat cognitive disorders including AD. Thus, there is evidence that alterations in the generation of neural network activities is involved in several cognitive disorders (for a review, see [41]), including in AD [42–46]. This paper will summarize the evidence regarding the role of Aβ in neural network dysfunction and cognitive decline but will not delve into the possible cellular mechanisms involved since they have been recently reviewed in great detail [1, 2, 5, 6, 8, 9]. Instead, I will highlight the fact that Aβ-induced neural network dysfunction plays a major role in AD and that the study of this process in animal models in vivo and in vitro can be expected to offer relevant insight into this disease and reveal therapeutic targets against AD-related cognitive decline.

2. Alterations in Different Neural Network Patterns Induced by Aβ

Since the generation of different patterns of neural network activity is a prominent feature of several circuits during their involvement in cognitive functions such as memory and learning [23, 24, 47], it is not surprising that alterations in such patterns of activity have been identified in AD patients, whose main manifestation of this disruption is the so-called “EEG slowing” [42–46]. The EEG slowing is observed in the early stages of AD and parallels the cognitive decline observed in these patients [42–46]. Interestingly, similar changes in EEG activity have been observed in transgenic animals that develop an AD-like phenotype through the over-production of Aβ [48–50]. A great deal of evidence

![Figure 1: The amyloid beta-peptide disrupts neural network activity along with cognition. The scheme in the middle represents a putative neural network containing neurons with different intrinsic properties (represented in different colors) that interact through synaptic connections (represented by lines). In the case of the hippocampal CA1 network the pyramidal cells, represented by the red circles, interact with each other but also with different populations of GABAergic interneurons, represented by the green and blue circles, to generate different patterns of population activity during cognitive processing. Of course, the generation of oscillatory activity by this network is required during normal cognitive processing (right, upper trace) [23–26, 37], whereas the alterations in such oscillatory activity (lower trace) produced by amyloid beta-peptide have been associated with cognitive deficits [20, 21]. The question mark represents the current search for the cellular mechanisms underlying such disruption. The traces on the left are recordings of hippocampal oscillatory activity obtained in vitro before and after bath application of amyloid beta-protein 30 nM. The photographs at the top and bottom represent a mouse during a test session of the passive avoidance paradigm. During such a session, control animals tend to remain in the illuminated compartment due to the fact that on the previous day they received an electric shock in the dark compartment. Animals with disrupted memory tend to cross into the dark compartment, as already proven for amyloid beta-application in this paradigm [38, 39]. In summary, the figure represents the relationship between normal cognitive processing and the generation of specific neural network activities as well as the fact that amyloid beta-protein disrupts both of these interconnected processes.](image-url)
points towards a causal role for Aβ in the induction of the neural network dysfunction just described. Experiments from my lab, and others, have shown that some features of the EEG slowing, as well as the cognitive disruption associated with it, can be reproduced by acute application of Aβ in rodents [20–22, 34–36, 51]. However, the evidence obtained from these experiments indicates that the effects of Aβ on the neural network activity are not uniform and, in some rare cases, can be even contradictory. Such “inconsistencies” have also been detected in studies of the oscillatory activity in AD patients. On the one hand, such patients exhibit an increased theta rhythm at rest [42–46], but a reduced induced-theta rhythm during particular cognitive challenges [52]. These observations suggest that the differences in the abnormal neural activity observed in AD as well as the diverse changes in the network activity induced by Aβ may be attributed to the great variety of neural network activity patterns generated by different neural networks throughout the brain and their differential sensitivity to the alterations induced by Aβ [53–55].

3. Alterations in Theta and Gamma Rhythms Induced by Aβ

As mentioned, theta rhythm oscillations have been closely related to different cognitive processes both in rodents [24] and humans [40]. Several groups, including ours, have reported that a single intracerebral injection of Aβ induces an acute as well as a long-term reduction in theta rhythm generation [20–22, 34–36], which in turn induces cognitive dysfunction [20–22]. Moreover, we and others have taken this finding a step further and have shown that acute application of Aβ in vitro induces a reduction in various neural network patterns including theta rhythm [51, 53, 56, 57]. In agreement with these findings, several transgenic mice that overproduce Aβ, and that exhibit cognitive decline, have shown alterations in theta rhythm generation [14, 48–50, 58]. In transgenic mice expressing the amyloid precursor protein containing the Swedish mutations (K670N, M671L; APPswe), a higher theta/delta ratio was found during the non-REM period of the sleep-wake cycle [58]. The double transgenic mouse expressing APPswe and mutated presenilin 1 (A246E) show enhanced theta rhythm during wakefulness and REM sleep [49], an observation that was reproduced, for the theta rhythm during REM sleep, by the same group in other AD transgenic mice that expressed the APP containing the Swedish and London mutations (V717I), the mutated presenilin 1 (A246E), as well as the TAU protein double mutant P301L and R406W, called the PLB1 transgenic mouse [14]. In contrast, the double transgenic mouse carrying the APPswe and presenilin 1 (G384A) mutations showed an age-dependent decrease in theta hippocampal activity elicited by brainstem stimulation [50]. Similarly, a significant reduction in theta oscillations was observed in other double transgenic mice carrying the APP697 mutations K595N and M596L as well as the mutated presenilin 1 (A246E) [48].

4. Other Alterations in Neural Population Activity Induced by Aβ

Besides electrophysiological means, neural network activity can also be analyzed through functional multi-neuron
calcium imaging, which allows the evaluation of neural network dynamics with single-cell resolution [34, 65]. Using this approach, it has been found that medial septal neurons lose their theta firing coherence upon Aβ application [66]. This effect has been evaluated in cultured neurons that exhibit synchronous spontaneous calcium transients [67–70], showing that either increasing Aβ production by transfecting the cultures with the human APP gene [69] or by directly applying Aβ to the culture medium drastically reduced the synchronized neuronal calcium oscillations [67, 68, 70]. Recently, calcium imaging has also been used in vivo to evaluate neural activity, either in the hippocampal CA1 region or in the cortex of the double transgenic mice expressing APPswe and mutated presenilin 1 (G384A) [30, 31]. These studies revealed that neural networks located in the proximity of "senile plaques" are profoundly disturbed and exhibit both an increase in the number of silent neurons as well as an increased number of hyperactive ones [30, 31]. Interestingly, in one of these studies, the direct application of Aβ induced an increase in neuronal calcium transients that lasted for few seconds [31]. In contrast, in our hands, application of Aβ to hippocampal slices induced a reduction in the number of cells that exhibited calcium transients within a few minutes. The neurons that remained active in the presence of Aβ showed a frequency of calcium transients similar to that in control conditions [34].

Patch clamp recordings have demonstrated that Aβ disrupts synchronized synaptic activity in the prefrontal cortex depending on the concentration of the peptide and the duration of application [33]. Application of a low concentration of Aβ (1 nM) inhibits synchronized activity, whereas application of a higher concentration of Aβ (500 nM) induced a biphasic effect that consisted of an initial decrease in network activity followed by an overexcitation [33]. An opposite finding was observed in neural networks cultured on multielectrode arrays, where Aβ application can produce an acute and transient reduction in neural network activity. However, if Aβ exposure is maintained for several hours (24 h) the Aβ-induced inhibition of neural network activity is reversed, and the activity becomes indistinguishable from the control [71]. All these findings clearly show that the effects of Aβ on neuronal network activity can be time and concentration dependent. It is possible that during prolonged Aβ exposure the peptide loses its ability to inhibit neural network activity through enzymatic degradation or sequestration into plaques. On the other hand, Aβ could lead to differential changes in neural network activity (even overexcitation) by forming aggregates with different sizes that produce differential effects on network activity [53]. Alternatively, it is possible that neural networks can adapt their activity to the presence of Aβ by changing their properties to compensate for the inhibitory effects produced by Aβ. In fact, in some cases, deregulation of such compensatory changes could lead to the generation of aberrant hyperexcitable states, such as those observed in several AD transgenic mice.

5. Induction of “Aberrant Activity” by Aβ

Some reports that characterized the EEG activity throughout the sleep-wake transitions in certain strains of AD transgenic mice found no evidence for epileptiform activity [14, 49, 58]; however, other long-term EEG recordings of several lines of AD transgenic mice have revealed spontaneous, nonconvulsive epileptiform discharges that, in some cases, contributed to sudden death in these animals [32, 72–74]. The generation of epileptiform activity has also been correlated with cognitive decline in several of these transgenic mice [60, 72, 73]. Interestingly, recent findings have shown that the epileptiform activity emerges during periods of reduced gamma oscillatory activity and that both the epileptiform activity as well as the cognitive deficits reported, in a transgenic mouse that expresses the APP with the Swedish and Indiana mutations (V717F), are corrected when gamma activity is re-established by genetic means [60]. In contrast, another recent study reported that the epileptiform activity observed in the double transgenic mouse expressing APPswe and presenilin 1 with deleted exon 9 correlates with increased fast oscillatory activity in the thalamocortical network [75].

In contrast to the evidence just reviewed, there is other evidence indicating that, instead of having a proepileptic effect, Aβ may indeed reduce epileptiform activity. For example, it has been found that slices taken from APPswe transgenic mice have a reduced frequency of epileptiform synchronous events induced by 4-aminopyridine [76], which is a strong proconvulsant both in vivo and in vitro [77–79]. Moreover, Aβ was shown to reduce epileptiform activity induced in vitro by chronic blockade of GABAergic inhibition [80]. Again, the explanation for these different effects of Aβ on distinct neural network activities can be found in the diversity of epileptiform states that networks can evolve into or in the various compensatory changes induced by the presence of Aβ.

6. Conclusions

The data summarized in this paper support the notion that a major component of Aβ-induced cognitive decline is the alteration of diverse neural network activity patterns. The experimental findings described here clearly indicate that the EEG slowing observed in AD patients can be reproduced both in vivo and in vitro in animal models of AD, which represent an excellent opportunity to study the cellular mechanisms involved in cognitive decline as a way to reveal therapeutic targets for AD. Of course, the evidence shows that the effects of Aβ on neural network activity are rather complex and depend on its concentration and conformation, as well as the duration of its application. However, such complexity, if well characterized, would provide evidence of specific cellular mechanisms affected by Aβ that would be essential for most, if not all, of the disturbances of neural network activity produced by this peptide. It is likely that several of the seemingly contradictory Aβ-dependent effects represent different elements of the same causal chain or, alternatively, that they represent independent branches of a more complex pathogenic process. Since Aβ produces
a strong deleterious effect on neural networks, it is likely that several strategies would develop to compensate for the inhibition produced by Aβ and that, in some cases, the failure of such adaptive changes would lead some networks to more disruptive states (hyperexcitation). Of course, it would be essential to determine which of the diverse effects of Aβ on neural network activity account for the cognitive dysfunction observed both in animal models and in AD patients.

Finally, the study of Aβ-induced neural network dysfunction offers an important, alternative view for the understanding of AD pathology. This pathological process, which does not necessarily involve neurodegeneration in its early stages, would provide an experimental model to test pharmacological or nonpharmacological means to prevent such network disruption. For instance, it has been shown that reestablishing gamma oscillation by overexpression of the Nav1.1 channel reduces the aberrant epileptiform activity and the cognitive decline in the transgenic mouse expressing the APP with the Swedish and Indiana mutations [60]. Similarly, the normalization of the EEG in the APP+/transgenic mouse, by passive Aβ immunization, correlates with a reduction in the circadian rhythm alterations observed in these mice [58]. Moreover, the reduction in the epileptiform activity with several antiepileptic drugs reduced cognitive dysfunction in AD transgenic mice [74, 81]. It has also been shown that lowering arachidonic acid levels by inhibiting the activity of group IVA phospholipase A2 reduced the effect of Aβ on neural network activity and prevented Aβ-dependent cognitive deficits in transgenic AD mice that expresses the APP with the Swedish and Indiana mutations [82]. Finally, we have recently reported that the inhibition of GSK-3 either with a specific inhibitor or with lithium, which is already in clinical use for the bipolar disorder [83], abolishes the inhibitory effect of Aβ on the generation of beta-gamma activity in the entorhinal cortex. This and other observations support the use of lithium in the treatment of AD [57]. These are just some examples of the promising venue that has been opened by investigations of neural network disturbances induced by Aβ. Whether or not these studies will render therapeutic approaches to treat AD, remains to be determined.

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