A INDUCES NEUROTOXICITY BY A PORE-FORMING MECHANISM SIMILAR TO OTHER PORE FORMING PEPTIDES

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We have recently postulated that the initial step in synaptic failure induced by Aβ is the consequence of membrane-pore formation, similar to those produced by other membrane acting compounds. Here, we compare the properties of Aβ and gramicidin, a classical pore forming peptide, with the aim of identifying common functional and structural features that may influence Ab toxicity. Both peptides formed β-sheet structures, as detected by staining with Thioflavin S. Interestingly, electron microscopy showed that gramicidin in aqueous solution was able to form fibrillar complexes resembling Aβ aggregates. Using perforated patch clamp recordings, we found that Aβ and gramicidin have pore-forming properties in neuronal membranes. On the other hand, unlike Aβ, gramicidin perforations displayed similar ion selectivity at 15 and 30 min of exposure, suggesting a more stable perforation than Aβ. Aβ perforations, on the other hand, displayed more complex selectivity supporting the late formation of a non-selective pore. For example, combined patch clamp-image recordings using pipettes filled with ethidium bromide showed that this large molecule was able to enter into the neuron in parallel with the increase in membrane conductance supporting the existence of a large perforation induced by Ab.

In conclusion, the present data comparing the effects of Aβ and a prototype membrane perforation inducer indicate that Aβ and gramicidin can form membrane perforations of different sizes and ion selectivity suggesting that Aβ causes ionic dyshomestasis in the brain of AD patients.