Dissecting the neuroprotective role of neurosteroids in Alzheimer’s disease: Modulation of bioenergetics and amyloid-ß/tau toxicity

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Dissecting the neuroprotective role of neurosteroids in Alzheimer’s disease: Modulation of bioenergetics and amyloid-ß/tau toxicity

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Research Abstract
Data from multilevel approaches indicate that neuroactive steroid hormones (neurosteroids) can promote neural health whereas their decline or absence are associated with decline in neural health and increased risk of neurodegenerative disease including Alzheimer’s disease (AD).

Among the steroids in decline is allopregnanolone (APa; a metabolite of progesterone) which was found to be reduced in the serum and brain of aged compared to young subjects. Moreover, AD patients showed an even further reduction in plasma and brain levels of APa relative to age-matched controls. In AD mice models, treatment with APa was able to reverse neurogenic AD deficits. More recent data revealed that APa was able to prevent cognitive deficits in transgenic mice when treatment started at pre-Aß pathology state. Based on the promising results obtained with APa in transgenic AD mice, we started a collaboration with A.G. Mensah-Nygan (Strasbourg; France) to test four different analogues of APa (patent holder: A.G. Mensah-Nygan), which exhibited neuroprotective and/or neurogenic effects in spinal cord injury. Notably, our preliminary findings show that the APa analogues exhibited superior effects on ATP homeostasis when compared to the mother compound APa.

Main working hypothesis

Based on our previous and preliminary findings, we hypothesize that neurosteroids especially APa and its analogues have a beneficial impact on tau/Aß-induced deficits in bioenergetics as well as dendritic processes and lead to a reduction of tau and Aß pathology in AD models.

For this approach, we will combine analyses in cell culture systems as well as transgenic mouse models. To identify the most promising APa analogue we will start in cellular systems that share key features with the in vivo models. While some evidence is provided for neuroprotective effects of neurosteroids, mainly APa, on Aß pathology, we are not aware of a single study well characterizing the effects of neurosteroids on tau pathology. Moreover, several studies investigated the modulation of bioenergetics by estrogen, our preliminary results, however, showed that this mode of action was not unique to estradiol, but was also relevant for APa.

Thus, we would like to pursue four different objectives as part of this program:

Aim A: We will firstly investigate the modulating effects of APa and its analogues in the presences of one pathological AD hallmark alone (overexpression of tau or APP). Thus, we will gain insights into the mechanisms interfering with tau-induced deficits in comparison with those of Aß.

Aim B: Secondly, by using an innovative TALEN approach we will investigate the effects of APa and its derivates on tau distribution, aggregation and cellular function.

Aim C: Thirdly, we will determine whether APa and one of its analogues (selected after completion of in vitro screening) show similar beneficial effects on deficits in tau transgenic mice (pR5) in vivo and hamper the synergistic destruction caused by the combination of Aß and tau in vivo (APP23xpR5) in collaboration with J. Götz (Brisbane, Australia).

Aim D: Fourthly, we will characterize the mode of action profile of APa in comparison with those of other neurosteroids (estradiol, testosterone, progesterone, DHEA) in vitro.

The current approach opens up the opportunity to characterize promising therapeutic candidate/s for simultaneous promotion of bioenergetic function and neuritic processes to prevent or delay further progression of AD pathology.

Further information available at:

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