Commentary

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Oestrogen Downregulates BACE Protein in Human Cell Culture: What Does This Teach Us about Alzheimer's Disease?

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The purpose of this short commentary is to add some thoughts on a particular aspect of the very interesting article by Dr. Csöregh Nord et al. [1] which has recently appeared in *Neurodegenerative Diseases*.

Postmenopausal oestrogen depletion is a well-known risk factor for Alzheimer's disease (AD). Previous studies suggest that oestrogen negatively regulates the level of amyloid β (Aβ) in the brain, but the molecular mechanism is largely unknown. Quite recently, the Aβ-degrading enzymes, insulin-degrading enzyme [2, 3] and neprilysin [4], have been identified to be upregulated by oestrogen, which in part might explain the beneficial effects of oestrogen in AD [2]. Csöregh Nord et al. [1] have now convincingly shown that oestrogen is involved in the regulation of gene expression of the putative α- and γ-secretases TACE (tumour-necrosis-factor-α-converting enzyme) and presenilin. Even more importantly, BACE [β-site of amyloid-precursor-protein (APP)-cleaving enzyme] protein expression (but not the gene coding for BACE) was demonstrated to be significantly downregulated by oestrogen treatment in mixed human neuronal/glial cell cultures. Csöregh Nord et al. [1] conclude that oestrogen may affect APP processing directly by regulating the expression of the involved enzymes. In particular, since BACE is regarded the principal β-secretase, its downregulation by oestrogen might be a way to effectively reduce Aβ burden via reduced β-secretase cleavage activity [1]. This is in line with another recent paper showing that in an early-onset AD transgenic mouse model expressing double mutant APP (Swedish: K67ON/M671L; Indiana: V717F) undergoing treatment with 17β-oestradiol, significantly lower levels of APP processing via β-secretase are detectable [3]. The question, however, is: does this new knowledge about the downregulation of BACE by oestrogen really help us much in understanding (and treating) APP processing in AD? Undoubtedly, the vast majority of cases of AD are sporadic (late onset) in origin. Patients suffering from sporadic AD possess a non-mutated ('wild-type') APP. Remarkably enough (and largely ignored in the literature), Hook's group could show that the activity of the 'established' β-secretase BACE1 for wild-type APP is extremely low, while other proteases (especially cathepsin B) are much more effective in cleaving APP at the wild-type secretase site [5–7]. Thus, cathepsin B could be another putative β-secretase candidate (or even the dominating one) in sporadic AD [5–7]. If so, we also have to ask about a possible effect of oestrogen treatment on cathepsin B. Unfortunately, we are not aware of any data about oestrogen-induced changes in brain cathepsin B activity or expression, but find-

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ings from non-neural tissues indicate that cathepsin B becomes upregulated under the influence of the hormone [8, 9]. Hence, it would be very interesting to look for the oestrogen-dependent expression of the alternative (or additional) β-secretase cathepsin B in the neuronal cell system used by Csöregh Nord et al. [1] in their study. If brain-associated cathepsin B is really upregulated under the influence of oestrogen, whereas BACE expression is downregulated, an elevated (and not a reduced) β-secretase activity might result in cases of sporadic AD. However, due to the effects which oestrogen has on α- and γ-secretases [1] as well as on Aβ-degrading enzymes [2–4], the net effect of the hormone on amyloid burden would probably still be a reduction, which would fit with observations previously made [1, 3].

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