

P004 Hypoxic Modulation of Amyloid Production in Primary Cultures of Rat Cortical Astrocytes: A role for β -Secretase (BACE1)?
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Prolonged periods of hypoxia are damaging to higher brain functions and lead to an increase in the likelihood of developing degenerative dementias such as Alzheimer's disease (AD). We have previously shown that chronic hypoxia (CH; 2.5% O₂, 24 hr) has a variety of effects, not only on neurones, but also on rat cortical astrocytes. These include alterations in Ca²⁺ homeostasis and, importantly in relation to AD, an increase in the production of immuno-reactive amyloid β -peptides. This could be due to increased BACE1 expression/activity resulting in greater amyloidogenic processing of APP. Surprisingly, CH did not result in any increase in mature β -secretase expression relative to normoxic astrocytes although there was a large rise in the 70kD/65kD ratio. A similar result was obtained with astrocytes treated with a hypoxia mimetic, the hypoxia inducible factor (HIF) stabilising compound FG-4496. An alternative mechanism to account for the increase in A β Ps might be the recent observation in neuroblastoma cells that CH reduced the expression of ADAM10, a putative α -secretase, and the production of sAPP α . If a similar inhibition of α -secretase activity occurs in astrocytes this might result in greater amyloidogenic processing.