Inhibition of GSK3β rescues hippocampal development and learning in a mouse model of CDKL5 disorder

This study from the University of Bologna investigates observations from their previous Cdkl5 mouse-model study. In that study (see review 30), the authors observed that in Cdkl5 knockout (KO) mice there is impaired neurogenesis and dendritic development (formation of nerve cells in the developing brain) which they proposed occurred through disruption of a signalling pathway known as the AKT/GSK-3β signalling pathway. Basically, GSK-3β is what is known as a "negative regulator" of neurogenesis – which means that as levels of GSK-3β increase, neurogenesis becomes impaired – something the authors had suggested explained the changes seen in Cdkl5 KO mice. In this study therefore, they investigated whether inhibiting GSK-3β activity in Cdkl5 KO mice could "rescue" these changes and return neurogenesis to normal.

The authors again studied hippocampal neurons whose development and maturation occurs shortly following birth. Something called SB216763 - or just SB – is a small molecule that is known to inhibit GSK3β activity. Therefore, in this study Cdkl5 KO mice were treated with SB – it was given to 20 day-old mice and continued for 25 days. There were essentially 3 groups of mice – a Cdkl5 KO group, a Cdkl5 KO group treated with SB and a control (normal) group. Histological changes within the brain were examined and any effects on behaviour of the mice studied.

Histological - the authors found that treatment of Cdkl5 KO mice with SB restored both neuron and dendritic morphology to that seen in the control mice. They also found restoration in the appearance of dendritic spines which therefore also suggested restoration of synaptic function (connections between neurons).
Clinical – the authors used 2 particular behavioural tests. For the learning and memory testing they found that compared to control mice Cdkl5 KO mice performed poorly. However, Cdkl5 KO mice treated with SB performed as well as the control mice. Cognitive function was also seen to improve in those Cdkl5 KO mice treated with SB.
Longer-term effects - encouragingly, improvement in both the histological and behavioural aspects of the treated Cdkl5 KO mice were maintained after cessation of treatment with SB. The authors point out, however, that GSK-3β itself acts on a number of substrates and so there may be many other factors involved in their observations in this study.

Note – this study is an excellent example of how developing an understanding of the molecular pathways in which CDKL5 is involved might eventually lead to therapeutic options. As the authors point out although SB itself is not being tested clinically, other inhibitors of GSK-3β are being investigated in the treatment of various conditions including Alzheimer's disease and strokes. The hope is that other therapeutic strategies for treating the CDKL5 Disorder can be developed through this type of research.