Supporting CDKL5

Dendritic Spine Instability in a Mouse Model of CDKL5 Disorder is rescued by IGF-1

This is a really interesting piece of research involving a number of centres in Italy. The study looks at the structural dynamics of dendritic spines, synaptic function and plasticity in Cdkl5 KO mice. They also present some electrophysiological studies including results of studies on something called long-term potentiation (LTP) – see explanation later..! They then examined the effect of treatment with IGF-1 on these parameters.

Studies were based on direct observations and electrical studies of the somatosensory cortex of the mice – that part of the cortex responsible for our sensory perception. Access for their observations was acquired through a surgically created window through which the cortex of the brain could be directly visualised – interesting! This allowed the authors to study – sort of almost in real time - differences in dendritic development between Cdkl5 KO mice and controls. Various histological observations were made at different stages of development.

Histological – In keeping with previous reports, the authors observed significantly lower dendritic spine density in Cdkl5 KO mice compared to controls. Through studying something called PSD-95 and showing that its activity was reduced, the authors were also able to determine that Cdkl5 deletion causes a loss of excitatory synaptic contacts between neurons (see The CDKL5 Protein for some background about this).

Synaptic pruning is a term used to describe a reduction in neuronal structures that occurs normally in the developing brain. The authors found that Cdkl5 is crucial in limiting short-term pruning during neuronal development in younger mice (27-28 days old). The authors also studied how dendritic spines evolved over a 30 day period from 50 days of age onwards – when the mice are considered as adults. They found that there was a significantly greater reduction in the numbers of spines in the Cdkl5 KO mice compared to control mice suggesting that dendritic spines in Cdkl5 KO mice are less stable. Furthermore, those spines still present in the Cdkl5 KO mice appeared immature - something that has been noted in previous studies. In particular, they observed that spines are longer, suggesting that Cdkl5 has a role in limiting their lengthening process – something that has been highlighted before (see review 21). It appears that in Cdkl5 KO mice although dendritic spines are being formed at a normal rate, they are not stable and are subsequently eliminated at a relatively higher rate than normal. This therefore shows that the long-term survival of dendritic spines is impaired in Cdkl5 KO mice.

Electrical – Long term potentiation (LTP) is an electro-physiological process that occurs between neurons and is thought might underlie the basis of learning and memory. In this study the authors found that LTP was dramatically impaired in Cdkl5 KO mice.

Treatment with IGF-1 – Insulin-like Growth Factor 1 (IGF-1) is a protein involved in the AKT signalling pathway which has already been implicated in the CDKL5 Disorder (see reviews 30 and 37). IGF-1 has been used to treat mice with MeCP2 gene mutations and so it was considered an appropriate molecules to study in CDKL5. The authors found that many of the abnormalities observed in the Cdkl5 KO mice were corrected by IGF-1. Interestingly, the Cdkl5 KO mice were found to have normal levels of IGF-1 and so the effects of the extra IGF-1 would appear to be through its action on other defective molecular pathways. Furthermore, the improvements seen in spine density were maintained 20 days after the end of treatment with IGF-1, suggesting these improvements might be long lasting.

Note – lots of technical stuff again to get through. This has some similarities with review 37. It is studying the effects of CDKL5 defects, in this case the effects on morphology and synaptic function, and then studying how these changes can be reversed through the addition of another protein – in this case IGF-1.

A cautionary thought - IGF-1 itself is not thought to be deficient in CDKL5 and it is postulated that the reversal of defects seen in this study occur because those molecular pathways that are defective as a result of a CDKL5 mutation are bolstered up by the addition of extra IGF-1. We are aware just from observations of CDKL5 that too much of something can be as bad as too little of something. Therefore, although the observations here might eventually lead to a therapeutic strategy for treating CDKL5, I imagine we have to be wary that increasing the levels of something like IGF-1 above normal does not produce detrimental effects elsewhere which may not have been detected or apparent in this particular study. At the end of the day we still need to understand the molecular pathways of CDKL5 – just saying!