In the news

ANTIPSYCHOTIC USE FOR AD QUESTIONED

Delusions, hallucinations and aggression are symptoms of Alzheimer's disease (AD) that are as traumatic as memory loss for the sufferers. To make matters worse, a US study finds that many antipsychotics commonly prescribed to alleviate these symptoms provide little benefit.

Although the drugs are not approved for AD in the US, many doctors prescribe them on the basis of their therapeutic effects in schizophrenia. However, Lon Schneider of the University of Southern California, the lead author of the study, says that "Most patients are not benefiting" (*Washington Post*, 12 October 2006) and that "…their tendency to cause intolerable side effects … offsets their benefits" (*Reuters*, 11 October 2006). The study, published in the *New England Journal of Medicine*, investigated three second-generation antipsychotics, finding no significant differences in the improvement of symptoms in comparison to a placebo.

Focusing on the need for better medications, Thomas Insel, Director of the National Institute of Mental Health, which funded the research, says that "These drugs are clearly not the answer" (*New York Times*, 12 October 2006). They might have some use, but treatment periods should be limited and should stop if side effects emerge, according to Jason Karlawish of the University of Pennsylvania (*Washington Post*, 12 October 2006). Bruce Kinon, a psychiatrist at Eli Lilly, which manufactures one of the drugs, agrees that "…treatment needs to be done with a lot of forethought and constant reevaluation" (*New York Times*, 12 October 2006). Others claim that addressing triggers of aggression could be more effective; Gary Kennedy of the Montefiore Medical Center, New York, argues that "Working on these kinds of behavioural factors should always be the first line of treatment" (*New York Times*, 12 October 2006).

Katherine Whalley

DEVELOPMENT

Neuroligin knockouts: form but no function

Setting up the brain's neural circuitry during development requires the correct construction and function of the synapses. New work by Frédérique Varoqueaux and colleagues reveals that neuroligins, a family of postsynaptic cell adhesion molecules, considered essential for building synapses, are in fact necessary only for subsequent synaptic maturation and function.

Neuroligins are crucial for proper brain function, shown by the fact that mutations to the human genes are associated with autism and mental retardation. Recent findings have indicated a functional role for neuroligins in synaptogenesis. For example, RNAi knockdown of neuroligins in cultured neurons has been shown to lead to the formation of fewer synapses, whereas their overexpression leads to more synapses. In addition, neuroligins are thought to be important for synapse maturation and function.

To investigate the *in vivo* role of these important molecules, Varoqueaux's team generated neuroligin-null mice. Of the four neuroligins in the mouse (NL1–4), NL4 is not detectable in newborn mice and is found only at extremely low levels in adult mice. Therefore, the team concentrated on NL1, 2 and 3, and made individual, dual and triple knockouts of the genes.

Mice lacking any one of the three genes seemed generally normal, as did the dual knockouts, although the latter showed reduced reproduction and drastically impaired parenting. However, mice lacking all three neuroligins died from breathing difficulties approximately 1 day after birth. NLs 1–3 are coexpressed in almost all neurons, and only the triple knockouts were neonatally lethal, indicating that there is a large degree of functional redundancy. The group therefore focused their studies on the triple knockout phenotype.

Histological analysis of the brains of NL1–3 triple knockout mice revealed that knocking out all three genes had apparently no effect on the gross cytoarchitecture of the brain. The density and organization of neurons in the olfactory bulb, hippocampus, cortex and brainstem was normal. Given the predicted role of neuroligins in synaptogenesis, this was rather surprising. However, closer inspection of the synapses of neurons of the brainstem respiratory network (which controls breathing) confirmed their normal ultrastructure. Furthermore, expression levels of integral components of the synaptic contacts were comparable with wild-type mice.

However, expression levels of synaptic communication proteins such as vesicle markers were reduced, indicating aberrant synaptic function. Indeed, electrophysiological analysis of the brainstem respiratory network neurons revealed that GABA (γ-aminobutyric acid)-mediated/glycinergic and glutamatergic synaptic transmission was markedly decreased. Therefore, the loss of synaptic maturation and function rather than loss of synapses *per se* is likely to be the cause of neonatal lethality in these mice.

The reason for the discrepancies between this work and previous *in vitro* studies is not yet clear. However, the creation of these mice, including the individual and dual knockouts, provides an important and valuable resource for continued *in vivo* investigations into neuroligin biology and synapse function.

Ruth Williams

ORIGINAL RESEARCH PAPER Varoqueaux, F. *et al.* Neuroligins determine synapse maturation and function. *Neuron* **51**, 741–754 (2006)