News Editor: Matthew Thorne
m.thorne@elsevier.com

news

New drugs for bipolar disorder?

Treasa Creavin, t.creavin@elsevier.com

Lithium is used to treat bipolar disease (BD) – or manic depression – but patients can experience many side effects including tremors, cognitive impairment and weight gain. Now researchers, based at Merck, have identified genes that could help in the development of BD therapy with fewer side effects [1].

BD is one of the most common, severe and devastating psychiatric disorders. Because of its high rate of recurrence and suicide in young patients, it is a major public health concern. Indeed scientists predict that by 2020, depression will be the second greatest disease burden worldwide [2].

Gene chips

Although lithium is widely used to treat BD, its mechanism of action is poorly understood. However, lithium is known to inhibit inositol monophosphatase, and it is thought that depletion of the inositol levels in the brain is important for lithium's therapeutic efficiency. Using DNA microarrays – or gene chips – a team led by Philip Brandish identified genes that were activated when inositol was depleted in rat brain slices.

Of the 29 genes that they identified, two were particularly interesting as they suggest new methods of treating BD. *GPR88* – an orphan G-protein-coupled receptor – is expressed in the higher brain centres and so might have a role in higher brain function (e.g. behaviour). *ADCYAP1* encodes a neuropeptide signalling molecule PACAP and is located close to a BD risk locus on chromosome 18. The authors propose that modulating brain PACAP (pituitary adenylate cyclase-activating polypeptide) signalling represents a new opportunity in the treatment of BD.

PACAP pathway

While acknowledging that further experiments are needed to establish concrete connections between PACAP and the efficacy of lithium in BD, Brandish said that, 'Lithium is already a pretty good drug in terms of its efficacy, but a compound acting through something downstream like PACAP has the chance to be safer and better tolerated. In that sense, targeting the PACAP pathway could be better than lithium'.

'Lithium hits many pathways and systems in the body. Targeting the PACAP pathway could introduce specificity which leads to selectivity and reduced side effects' he added. 'There is a clear need to develop novel compounds for the treatment of bipolar disorder that have efficacy as well as a low burden of side effects. There is insufficient data to comment on the potential therapeutic value of modification of PACAP signalling in the brain, and one would need to be mindful of the possible adverse effects associated with this strategy', said Paul Mackin (University of Newcastle Upon Tyne, UK).

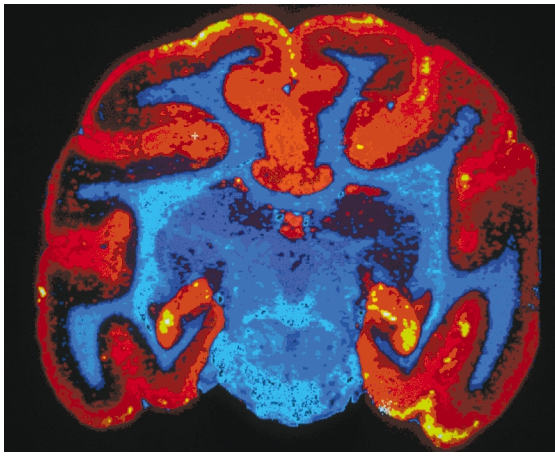
However, BD is phenotypically and genetically complex and many genes and pathways not investigated in this study are likely to be important. 'It will be interesting to test whether these genes are also regulated by lithium treatment and especially important to determine whether they are regulated by lithium or inositol *in vivo*', said Peter Klein (University of Pennsylvania, USA). Brain slices are readily depleted of inositol, but the reduction of inositol *in vivo* by lithium treatment is modest and most likely insufficient to interfere with synthesis of PIP2 (a precursor for IP3 and diacylglycerol). 'It will also be interesting to test whether other drugs used to treat BPD also regulate the expression of these genes', he added.

The results of Brandish's study are interesting and warrant further investigation. As the authors point out, several important questions remain, including whether PACAP levels in patients are different to those in controls; and whether changes in PACAP correlate with symptomatic relief.

References

1 Brandish, P.E. *et al*. (2005) Regulation of gene expression by lithium and depletion of inositol in slices of adult rat cortex. *Neuron* 45, 861–872

2 Murray, C.J. and Lopez, A.D. (1996) Evidence based health policy – lessons from the global burden of disease study. *Science* 274, 740–743



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