MOOD DISORDERS

Channel inhibitor shows antidepressant potential

The molecular mechanisms underlying human depression are still poorly understood. At present, most drug therapies for this disorder exert their effects by enhancing monamine neurotransmission, but the onset of symptom relief is slow, and many patients fail to achieve full remission. Writing in the *Journal of Neuroscience*, Wemmie and colleagues now provide evidence that inhibition of the amiloride-sensitive cation channel 2, neuronal (ACCN2; also known as ASIC1A) could be a novel strategy for the treatment of depression.

ACCN2 is ubiquitously expressed in the nervous system, and high levels have been reported in the amygdala, a brain region that is implicated in mood regulation. Previous studies have shown that ACCN2 knockout mice exhibit reduced anxiety-related behaviour (such as an attenuated fear response) and decreased neuronal activity in the amygdala. Here, the authors showed that ACCN2 knockout mice exhibit reduced depression-related behaviour, as assessed by monitoring sucrose preference following stress, and performance in the tail suspension test and the forced swim test, which are thought to parallel anhedonia and the lack of motivation and energy observed in patients with depression.

In agreement with these findings, intracerebroventricular injection of reversible ACCN2 inhibitors (either the tarantula-derived peptide toxin PcTx1 or the small molecule A-317567) produced similar antidepressant effects to *ACCN2* gene disruption. Conversely, the antidepressant-like phenotype of ACCN2 knockout mice was eliminated by restoring ACCN2 expression in the amygdala with a virus vector.

As monoamine re-uptake inhibitors could still exert an antidepressant effect in ACCN2 knockout mice and serotonin depletion did not alter the antidepressant effects of ACCN2 inhibitors, the authors concluded that ACCN2 inhibition affects a novel pathway that is relevant to depression-related behaviour.

Stress and neurotrophic factors have also been implicated in depression, but the authors showed that the corticosterone response to stress in ACCN2 knockout mice did not differ from that in wild-type mice. Interestingly, however, the stress-induced decrease in brain-derived neurotrophic factor (BDNF) levels in the hippocampus, which is known to be blocked by antidepressants and electroconvulsive therapy, was absent in the ACCN2 knockout mice.

In summary, this study not only identifies a potential new target for the development of drugs to treat depression, but also hints at a distinct mechanism from that of currently approved drugs to combat this disorder. The link between ACCN2 and BDNF may also have wider therapeutic implications as both molecules have been associated with neurodegenerative disorders.

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ORIGINAL RESEARCH PAPER Coryell, M. W. *et al.* Acid-sensing channel 1a in the amygdala, a novel therapeutic target in depression-related behaviour. *J. Neurosci.* **29**, 5381–5388 (2009)