

Neuro-endocrinology

BRIEFINGS

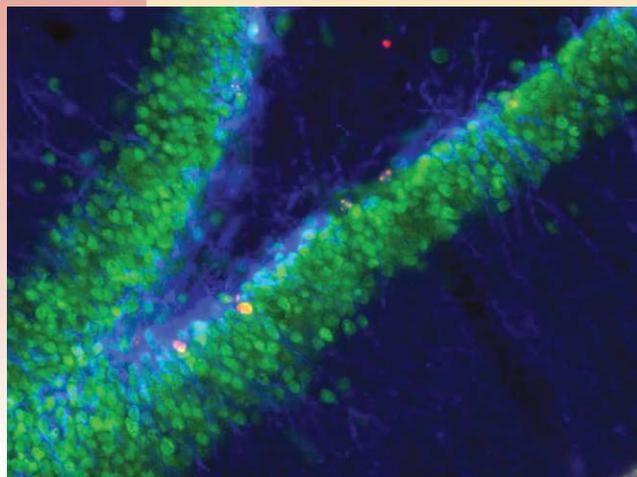
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SUMMARY

Pieces of evidence are emerging in support of the startling idea that the birth of new neurons in the adult brain in some way underlies major depression. Although there are intriguing parallels between factors which regulate neurogenesis and those predicting depression or its recovery, at this point we should remain sceptical but allow cautious hope that more effective therapies may be suggested.

Neurogenesis in the dentate gyrus. The yellow cells are dividing progenitors; green cells are adult (mature) neurons, and blue cells are immature neurons.

(G-J Huang and J Herbert)



NEUROGENESIS AND DEPRESSION: BREAKTHROUGH OR BLIND ALLEY?

Genesis of an idea

In 2000, Jacobs and colleagues proposed in the journal *Molecular Psychiatry* the novel theory that altered rates of neurogenesis (birth of new neurons) in the adult hippocampus might underlie either the development of major depression or recovery from it. Depression, like other mental illnesses, is currently diagnosed on symptoms alone, as is the response to treatment. The lack of an objective diagnostic index, let alone a convincing neural basis for depression, is a huge obstacle to clinical practice and to developing new strategies for either treatment or prevention of this common, devastating, illness. So the neurogenesis suggestion could represent the first glimmer of a new avenue: one leading to a more coherent understanding of depression, as well as more targeted and effective therapeutics.

How did the idea arise? New neurons are formed from progenitor cells in the inner layers of the dentate gyrus, an area within the hippocampus, the 'sea-horse' shaped brain structure traditionally implicated in learning and memory. Only about half the new neurons survive, but those that do receive inputs and make connections and are thus integrated into the adult-type circuitry. Most importantly, neurogenesis is highly labile. Stress and raised glucocorticoids decrease it, whereas exercise and, most intriguingly, anti-depressant drugs do the opposite. The ideas of Jacobs and colleagues were largely based on this, since high cortisol and adversity are risks for depression, whilst exercise and anti-depressants hasten recovery. However, all four have widespread actions in the brain and are certainly not limited to the dentate gyrus.

Anti-depressants

What about the experimental evidence? A major impetus occurred when it was shown that dentate gyrus neurogenesis, and also behaviour, failed to respond to the serotonin reuptake inhibitor, fluoxetine ('Prozac'), in mice lacking the 5HT1A serotonin receptor. Targetted radiation (which destroys the dentate progenitor cells) also prevented the behavioural effects of these drugs. But direct evidence can only come

from showing that either events causing depression depend upon reduced neurogenesis, or that increases are essential for 'anti-depressive' drugs to be effective. Anti-depressants commonly take 3-4 weeks to be clinically effective, even though their pharmacological actions occur within a few hours. New neurons in the hippocampus take about 28 days to mature and make connections: is this the basis of the therapeutic response? However, it takes about two weeks for fluoxetine to stimulate progenitor cell division, which suggests a latent interval in the dentate gyrus corresponding to the therapeutic response which still requires explanation.

Is there an experimental 'model' of depression? Here we have a real problem. The most commonly used behavioural techniques depend upon some measure of 'helplessness'. The animal is put into an adverse situation; initially it tries to escape, but ultimately it gives up. Its behavioural state is characterised as 'despair'. The time taken for this to happen is the dependent variable; anti-depressant drugs increase this interval. Many authors refer to inducing 'depression' by these methods. Since there is a good correlation between the activity of anti-depressants and clinical effectiveness, the argument is that this test is a valid one. But 'anti-depressant' is not a pharmacological description of drugs such as fluoxetine. Serotonin has a ubiquitous distribution in the brain, and a correspondingly wide influence on many behaviours and neuroendocrine functions. Parallel effects on two sets of data may only reflect the range of actions of serotonin. This is therefore not prediction but correlation. There are other problems: depression takes weeks to develop after an adversity in man, not minutes or even days as in

the animal tests. Finally, why 'despair'? This is a label: others (including 'adaptation' or 'learning') are equally plausible. Excessive reliance on these tests may be one reason why no truly new anti-depressants have been developed for several decades. The absence of a reliable 'model' of depression is a major handicap to substantiating any link between neurogenesis and depression.

The cortisol link

"The resolution of current scanners is insufficient to detect changes in neurogenesis during a depressive episode ..."

Is the hippocampus involved in depression? Much of the experimental literature on 'emotionality' points to other brain areas: the amygdala and, in primates, the orbital frontal lobe. Polymorphisms in the serotonin transporter increase the risk of stress-induced depression in man and alter fMRI-scan responses to emotional stimuli in both areas. The hippocampus is implicated in spatial or contextual learning and in episodic memory in man. There are reports of diminished hippocampal volume in depression, though whether this precedes illness or is a consequence is unclear. The resolution of current scanners is insufficient to detect changes in neurogenesis during a depressive episode, and limited post-mortem evidence has so far failed to show the expected correlation. Memory is altered in depression, and excessive 'rumination' (internal rehearsal of negative thoughts or events) predicts increased onset in adolescents. The hippocampus is

highly sensitive to cortisol, which not only decreases neurogenesis, but predisposes its pyramidal neurons to damage. Cortisol also accentuates the memory of adverse events, and persistently higher cortisol is a risk factor for depression in both adolescents and adult women. Polymorphisms in the neuronal growth factor BDNF are also associated with increased risk for depression in man. BDNF and its principal receptor are highly expressed in the hippocampus, and BDNF increases neurogenesis.

So: breakthrough or blind alley? Neither, at this point. The parallels between the multiple factors regulating hippocampal neurogenesis and those predicting depression or its recovery remain tempting, but the current evidence should be treated with positive scepticism and cautious hope. We are riding a roller-coaster, not a band-wagon.

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