PSYCHIATRIC DISORDERS

Tipping the cortical balance

Imbalance in the ratio of excitatory to inhibitory cortical activity may underlie the behavioural deficits that are observed in conditions such as autism and schizophrenia; however, this hypothesis has not been tested directly. Using novel optogenetic tools, Deisseroth and colleagues now show that in mice, an elevation in the excitation/inhibition ratio in the medial prefrontal cortex (mPFC) impairs cellular information processing and leads to specific behavioural impairments.

Although different genes have been linked to autism and schizophrenia, similar behavioural phenotypes, including deficits in social behaviour and cognition, have been associated with these conditions, suggesting that the underlying genetic abnormalities may converge on a common pathophysiological mechanism. Disruption of the excitation/inhibition balance in the cortex could be this mechanism, although a causal link between such cortical dysfunction and behavioural deficits has not been shown directly.

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Using optogenetics, Deisseroth and colleagues examined this link in mice. The authors developed a stable step-function opsin (SSFO) that caused membrane depolarization in cultured neurons for a sustained period of time after a single flash of light. They expressed SSFO in different neuronal mPFC populations: first in pyramidal neurons to modulate excitation and then in GABAergic parvalbumin-positive (PV^+) interneurons to manipulate inhibition. They then used whole-cell patch clamping to assess the effects of light-induced activation of this opsin on ongoing synaptic activity in slices.

SSFO activation in PV^+ interneurons decreased spiking in pyramidal cells through synaptic inhibition but had little effect on the intrinsic cellular information processing by the pyramidal cells, as measured in terms of their input–output characteristics. Interestingly, SSFO activation in pyramidal neurons increased spiking but caused a substantial reduction in information processing in these cells, highlighting the detrimental effects of elevated excitation.

The properties of SSFO allowed optogenetic manipulation to be combined with complex behavioural experiments in freely moving animals, and the authors examined the effects on social behaviour of modulating neuronal activity. Mice expressing SSFO in pyramidal cells or in PV^+ interneurons were subjected to a 2 s flash of light in the mPFC, after which the optical fibre was removed and the animals were exposed to a mouse of the same sex. Unlike mice expressing SSFO in interneurons, which showed normal levels of exploration of the newly introduced animal, mice expressing SSFO in pyramidal neurons showed no interest in their new companion, which is suggestive of a social interaction deficit.

Fear conditioning immediately after SSFO activation enabled the authors to examine whether a cortical excitation/inhibition imbalance could affect cognition. Strikingly, although animals expressing SSFO in interneurons exhibited conditioned responses resembling those found in wild-type animals, mice expressing SSFO in pyramidal cells showed no conditioned responses, which is indicative of impaired cognition.

Finally, the authors tested whether increased inhibition in the mPFC could negate the effects of elevated cortical excitation. To do so, they developed a novel opsin (C1V1) that could be activated by a different wavelength of light to that used for SSFO and hence allow combinatorial control of excitation and inhibition in the same mouse.

In the three-chamber social test, activation of SSFO expressed in pyramidal neurons led to a reduction in an animal's preference for the 'social' chamber. Interestingly, simultaneous activation of SSFO in these cells and of C1V1 expressed in PV^+ interneurons reduced this behavioural deficit.

Taken together, these findings suggest that an elevation but not a reduction in the excitation/inhibition ratio impairs social behaviour and cognition through a defect in cellular information processing. This mechanism may explain the similar behavioural deficits that are observed in autism and schizophrenia.

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