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PERSPECTIVES

Listening to Npas4: a transcription factor is the prescription for restoring youthful plasticity in the mature brain

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During development there exist specific time windows, known as critical periods (CPs), during which the brain can be rapidly and extensively altered by sensory experience. Notably, the shift in the relative ability of each eye to drive responses in the visual cortex, or ocular dominance (OD) plasticity, following monocular deprivation (MD) has proven to be a useful model for the investigation of developmental CPs. Early studies by Hubel and Wiesel in cats and primates showed that occlusion of one eye during postnatal development resulted in more neurons in the visual cortex responsive to the open eye and fewer driven through the closed eye, and these shifts in OD were not reversible in adulthood (Hubel & Wiesel, 1970). For many years following this discovery the general consensus was that if disorders due to early sensory deprivation, such as amblyopia, were not caught early enough there was little hope for regaining normal function later in life.

Interestingly, more recent studies in rodents have shown that the adult visual cortex has a greater degree of plasticity than initially thought (Sawtell *et al.* 2003). Experiments in mice have shown that OD plasticity can be induced during adulthood: MD in adult mice causes an enhanced response to stimulation of the non-deprived eye. Notably, this enhancement takes longer to occur and the depression of the deprived-eye responses, normally observed with MD in young animals, is absent in post-CP animals (e.g. >P35) suggesting that the mechanisms underlying adult plasticity may be different to those occurring in young animals.

In the adult visual cortex, it has also been shown that certain experimental manipulations can help reinstate a form of plasticity more closely resembling that seen during the CP. For example, a 4 week treatment with fluoxetine (FLX), the selective serotonin reuptake inhibitor more commonly known as Prozac, used to treat depression, has been shown to restore plasticity in adult rat visual cortex (Maya-Vetencourt *et al.* 2008). Determining the mechanisms by which juvenile-like plasticity can be reopened in adulthood is particularly interesting for designing clinical treatments of amblyopia and also holds exciting possibilities for learning and memory augmentation in adults. In this issue of *The Journal of Physiology*, Maya-Vetencourt and colleagues identify Npas4 as an important activity-regulated transcriptional factor that is both necessary and sufficient for reinstating plasticity in the adult cortex (Maya-Vetencourt *et al.* 2009).

The researchers noted that FLX treatment resulted in increased levels of Npas4 mRNA and protein expression. This prompted them to examine the consequences of Npas4 overexpression without FLX treatment. In animals virally overexpressing Npas4 in visual cortex, MD produced a profound OD shift, as demonstrated by a reduction in the visually evoked potential driven through the deprived eye. Importantly, no shift in OD was seen in Npas4-overexpressing animals that did not undergo MD, indicating that Npas4 does not non-specifically alter the properties of visual cortex neurons. Furthermore, the FLX-mediated shift in OD could no longer be induced when Npas4 was down-regulated by siRNA indicating that Npas4 is necessary for FLX to reactivate plasticity in adulthood. Whether Npas4 is specific to pharmacologically induced plasticity or might also participate in other experimental protocols (e.g. environmental enrichment, caloric restriction, dark exposure) that permit adult plasticity remains to be investigated. Moreover, determining whether Npas4 is also involved in regulating the onset and closing of early developmental CPs will be interesting.

Why did the authors of this study choose to focus on Npas4 rather than other transcription factors that have been linked to synaptic development such as CREB, MEF2, or NFAT? (West & Greenberg, 2011)

For one, the prevailing model of the opening of the CP for OD plasticity is based on the developmental regulation of the excitatory/inhibitory balance in visual cortex, with the maturation of inhibitory circuitry being the key transitional event (Hensch & Fagiolini, 2005). A recent study by Lin *et al.* (2008) demonstrated that the transcription factor Npas4 is an activity-dependent regulator of the number of functional inhibitory synapses that form on excitatory neurons. In this study, knockdown or conditional knockout of Npas4 in hippocampal pyramidal neurons led to decreases in the number of inhibitory synapses measured by immunocytochemistry and by electrophysiology, whereas overexpression resulted in more inhibitory synapses.

Another factor that makes Npas4 an appealing candidate for the regulation of adult plasticity is that it directly regulates the expression of brain-derived neurotrophic factor (BDNF), a molecule that has been clearly linked to multiple forms of synaptic plasticity and can also regulate inhibitory synapse maturation (Lin *et al.* 2008). This is particularly interesting as BDNF expression levels are increased in visual cortex of FLX-treated adult rats, which importantly exhibit decreased levels of GABA (Maya-Vetencourt *et al.* 2008). Consistent with a role for NPAS4 in regulating synaptic plasticity, a recent study has reported elevated NPAS4 expression in the hippocampus after contextual learning, and that knockout animals exhibit impaired contextual memory (Ramamoorthi et al., 2011)

Overall, there is compelling evidence that Npas4 expression increases inhibitory tone. So how does this fit into a model of enhanced adult plasticity, which at least in the case of FLX treatment appears to correlate with a decrease in inhibition? Maya-Vetencourt and colleagues speculate that FLX treatment causes a decrease in inhibition which in turn may lead to a compensatory increase in Npas4 expression that would promote the expression of various other plasticity-associated molecules, including BDNF. Although *in vitro* studies suggest that Npas4 may actually reduce the total number of functional excitatory synapses, additional *in vivo* studies will be needed to determine whether signalling downstream of Npas4 might influence rates of dendritic spine turn-over or induce metaplasticity at

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excitatory synapses in visual cortex that could explain the augmentation in OD plasticity observed.

Restoring juvenile levels of plasticity in the adult brain could have enormous therapeutic potential. A better understanding of how to modify the connectivity of neurons later in life will impact how we treat neurological conditions, from developmental disorders, to acute injury, to senile dementia, that were once considered untreatable.

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