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Regulation of synaptic plasticity in the mouse prelimbic cortex by α_7 nicotinic acetylcholine receptors.

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Learning and memory processes play important roles in the development of addiction-related behaviours. The prefrontal cortex (PFC) plays a key role in these behaviours. In particular the dorsal medial prefrontal cortex, or prelimbic cortex (PrL), has been implicated in promoting reinstatement to drug seeking behaviour (Van den Oever et al., 2009). Nicotinic acetylcholine receptors (nAChRs) have been shown to affect synaptic plasticity in a number of brain regions and the selective α_7 nAChR antagonist methyllycaconitine (MLA) inhibits reinstatement of morphine conditioned place preference (Feng et al., 2011; Wright et al., 2013).

To elucidate a potential mechanism for this, brain slice electrophysiology experiments were conducted in 5 week old C57BL/6 naïve mice. Field excitatory post synaptic potentials (fEPSPs) in the PrL were evoked and recorded from layer II/III and V respectively to measure stimulus induced long term potentiation and depression (LTP and LTD). LTP was evoked via a repeated theta burst stimulation whilst LTD was evoked via a 3Hz low frequency stimulation (Huang et al., 2004; Roder et al. 2003). Whole-cell voltage-clamp recordings of layer V pyramidal neurons were conducted to measure spontaneous inhibitory post synaptic currents (sIPSC) (Aracri et al. 2010). fEPSP amplitudes were normalised to baseline. 1 slice per animal was used within each treatment group. Statistical comparisons (unpaired Student's t-test) were made 60 minutes after LTP or LTD induction. Frequencies of spontaneous currents were compared using the Kolmogorov-Smirnov test.

Induction of LTP was significantly reduced by bath-application of 100nM MLA (control: 112±5%, n=8; +MLA: 97±3% n=5; $P<0.05$ total 10 animals). Surprisingly, MLA (100nM) also enhanced the inhibited induction of LTD (control: 98±8%, n=6; +MLA: 71±7%, n=6; $P<0.05$ total 10 animals). To observe the effect of α_7 nAChR activation on LTP and LTD the α_7nAChR positive allosteric modulator (PAM) PNU-120596 and selective agonist PNU-282987 were utilised. The combined presence of the PNU-120596 (10μM) and PNU-282987 (300nM) inhibited induction of LTP (control: 127±5%, n=9; +PNU-120596 / PNU-282987: 107±5%, n=5; $P<0.05$ total 12 animals). LTD induction was unaffected.

The frequency of sIPSCs were significantly increased in the combined presence of PNU-120596 (10μM) and PNU-282987 (300nM) (frequency increased by 148±26%; n=7 slices taken from 4 animals; $P<0.001$). This effect was reversed by MLA (100nM). In the presence of PNU-120596 (10μM) alone, sIPSC frequency was unaffected.

We have shown that both α_7 nAChR antagonism and activation can inhibit PrL LTP, whilst α_7nAChR antagonism, but not activation can enhance PrL LTD. We've also shown that α_7nAChR activation increases inhibitory tone on PrL layer V pyramidal

neurons, which may explain the observed effects on PrL plasticity. Overall these findings contribute towards a mechanism by which, α_7nAChR mediated synaptic plasticity may influence reinstatement to drug seeking behaviour.

Aracri P et al, Cerebral Cortex 20:1539, 2010

Feng B et al, Behav Brain Res 220:100, 2011

Huang YY et al, Proc Natl Acad Sci USA 101:3236, 2004

Roder S et al, Neuroscience 120:705

Van den Oever MC et al, Neurosci Biobehav Rev 35:276, 2010

Wright V et al, British Pharmacological Society meeting, 2013