which nAChR subtype mediated the facilitating effect of nicotine on LTP, recordings were performed in the presence of α7 nAChR agonist and antagonist: choline (10 mM) and MLA (100 nM), respectively. The application of choline (100 s) increased the EPSC and then a single 100 ms/100 Hz burst led to LTP. The co-application of nicotine with MLA (100 s) prevented switching form LTD to LTP. These results suggest that cholinergic stimulation mediated by nAChRs markedly potentiates synaptic transmission and long-term synaptic plasticity along the mossy fibre pathway of the cerebellum.

doi:10.1016/j.bcp.2009.06.052

2.2

Nicotinic acetylcholine receptors differentially regulate phosphorylation of dopamine target cell proteins in the rat prefrontal cortex

Phil D. Livingstone*, James Hockley, Susan Wonnacott

Dept. Biol. Biochem., Univ. of Bath, Bath BA2 7AY, United Kingdom

The prefrontal cortex (PFC) is an executive area of the brain critical for working memory and decision-making. Disorders such as schizophrenia and attention deficit hyperactivity disorder reflect in part an imbalance of prefrontal dopamine. Nicotine, via nicotinic acetylcholine receptors (nAChRs), facilitates dopamine release and enhances executive functions of this region [1], yet the downstream molecular consequences of nAChR-induced dopamine release remain to be fully elucidated. Here we examine the effect of stimulation of nAChRs containing either β2 or α7 subunits upon dopamine receptor D1 signalling pathways *in vitro* in PFC prisms (150 μm) using immunoblotting. Striatum was compared with PFC in parallel, because dopamine and cAMP regulated phosphoprotein of 32 kDa (DARPP-32), are known downstream effectors in this region [2]. Nicotine (100 μM) significantly increased phosphorylation of DARPP-32 at Thr34, indicative of increased cell excitability [2], in striatal but not PFC prisms. Blockade by mecamylamine and insensitivity to α-bungarotoxin (αBgt) supports a mechanism involving β2* nAChRs. This is consistent with comparable changes elicited by the β2* nAChR selective agonist 5-Iodo-A-85380. Activation of α7 nAChRs using choline (3 mM) co-applied with PNU-120596 (10 μM) significantly increased DARPP-32 phospho-Thr34 in PFC and striatum to a similar extent (68 ± 21 % and 75 ± 18 % above basal, respectively), sensitive to αBgt. Increased DARPP-32 phosphoThr34 was also observed in both regions in response to the D1 agonist SKF81297 (10 μM). AMPA receptors are key determinants of cell excitability. AMPA receptors were also significantly phosphorylated following treatment with nicotine, choline plus PNU-120596 or SKF81297 at Ser845, a site associated with increased cell surface trafficking [3], in PFC and striatal prisms. The D1 antagonist SCH23390 (1 μM) blocked all phosphorylation events described (DARPP-32 and $AMPA_R$). Total DARPP-32 and glyceraldehyde 3-phosphate dehydrogenase levels were unaffected by any treatment. These data suggest that PFC α7 nAChR activation facilitates dopamine release that via D1 receptors, increases $AMPA_R$ phospho-Ser845, possibly downstream of DARPP-32 activation. Nicotine-mediated increases in phospho-$AMPA_R$ relies on β2* nAChRs and does not involve DARPP-32. Cellular localization of these changes is under investigation. Elucidation of dopamine signaling in the PFC facilitated by particular nAChR subtypes is critical when viewing these receptors as therapeutic targets.*Acknowledgements*: Supported by BBSRC grant BBS/S/15600 to SW BBSRC Studentship to PL.

References

[1] Levin, et al. Psychopharmacol 2006;184:523–39.
[2] Svenningsson, et al. AAPS J 2005;7:E353–60.
[3] Ehlers. Neuron 2000;28:511–25.

doi:10.1016/j.bcp.2009.06.053

2.3

Nicotine activates a dopamine signal that enables *in vivo* synaptic plasticity of the kind that underlies associative memory

Jianrong Tang[1,*], John A. Dani[1,2]

[1] *Department of Neuroscience, Baylor College of Medicine, Houston, TX 77030, United States*
[2] *Menninger Department of Psychiatry and Behavioral Science, Baylor College of Medicine, Houston, TX 77030, United States*

It has been documented that nicotine induces synaptic plasticity in the hippocampus, which might underlie drug-linked memory that cues continued tobacco use. The hippocampus is an important center for contextual and spatial memory. It receives cholinergic inputs from medial septum and dopaminergic innervation from the midbrain dopaminergic systems. Nicotinic acetylcholine receptors (nAChRs) and dopaminergic receptors (DARs) are co-expressed in hippocampus, including the dentate region. Although DA–ACh interactions in the hippocampus have been reported to be critical for drug-associated memory, it is not known how dopaminergic signaling influences nicotine-induced synaptic plasticity at the physiological level. Here we examined the effects of long-range vs. local manipulation of dopaminergic D1- and D2-type receptors on nicotine-induced synaptic plasticity of the perforant path to the dentate gyrus of awake, freely moving mice. Field recordings from the hilar region of the dentate were measured in response to electrical stimulation in the medial part of the perforant path. The recording and stimulating electrodes were implanted 2-3 weeks before the tests. Acute application of nicotine (i.p.) dose-dependently induced long-term potentiation (LTP) in this pathway. Nicotine (at the biologically relevant dose of 1.0 mg/kg) caused a long-lasting potentiation of the evoked responses. When DA signaling was inhibited by systemic administration of D1-type receptor antagonist SCH23390 or D2-type agonist quinpirole, we found that nicotine-induced LTP was blocked. In contrast, D2-type antagonist eticlopride showed significant enhancement of the LTP induction. To further dissect the local vs. long-range effect of dopaminergic manipulation, SCH23390 was ipsilaterally infused into the dentate gyrus prior to nicotine. The nicotine-induced LTP was completely abolished by the inactivation of D1-type receptors in the dentate. Consistent with the need for an incoming DA signal from the midbrain, local infusion of nicotine in the dentate did not alter the synaptic plasticity along the recording pathway. Inactivation of the midbrain dopaminergic area by tetrodotoxin prevented the nicotine-induced plasticity in the dentate. Together, these results suggest that dopaminergic signaling serves as a functional label of salient events by enabling synaptic plasticity that underlies drug-induced associative memory.

Acknowledgements: Supported by NIH NIDA (DA09411) and NINDS (NS21229, NS048505).

doi:10.1016/j.bcp.2009.06.054