β2 SUBUNIT CONTAINING NICOTINIC ACETYLCHOLINE RECEPTORS MODULATE DOPAMINE RELEASE IN THE MEDIAL PREFRONTAL CORTEX IN RATS

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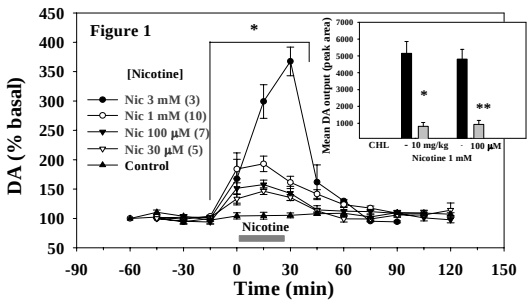
The prefrontal cortex (PFC) is regarded as the executive centre concerned with cognitive processing. Mesocortical lesions of dopamine (DA) afferents innervating the medial PFC (mPFC) produce deficits in attentional processing and working memory (Brown *et al*., 2002). Nicotine enhances these cognitive processes (Levin *et al*., 1998), possibly by facilitating DA release. To address this possibility we have characterized the local effects of nicotine on DA release from the mPFC using in vivo microdialysis in freely moving rats.

Adult male Sprague-Dawley rats weighing 300-320 g were anaesthetized (ketamine 75 mg/kg/i.p. and medetomidine 0.5 mg/kg/i.p.) and stereotaxically implanted with unilateral microdialysis probes (Brain link, Groningen, Netherlands, 4 mm active membrane) in to the mPFC (A/P 3.2, M/L 1, D/V 5 mm from bregma). Anaesthesia was reversed with atipamezole 1 mg/kg/s.c. and the dialysis was performed 24 hours later. The probes were perfused with artificial cerebrospinal fluid (aCSF, 2 μl/min) and 15 min fractions were collected and analyzed offline for DA by HPLC coupled to amperometric detection. All drugs were dissolved in aCSF unless otherwise specified, and infused via retrograde dialysis into the mPFC.

Local perfusion of nicotine for 30 min produced a concentration-dependent increase in extracellular DA levels ($p<0.0001$) (Figure 1). The long acting noncompetitive nAChR antagonist chlorisondamine (CHL) given by continuous local infusion (100 μM), or systemic administration (10mg/kg/i.p.) abolished nicotine (1mM) induced DA release ($p<0.05$, $p<0.01$) (Figure 1 insert). Nicotine-evoked DA release was partially attenuated by continuous local infusion of the β2-selective competitive nAChR antagonist dihydro-beta-erythroidine (DHβE, 10 μM) ($p<0.05$) (Figure 2).



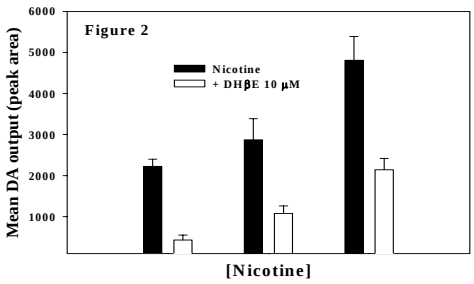


Figure 1 Effect of infusion of nicotine into the mPFC on extracellular DA levels. *$p<0.0001$ vs basal values (mean ± SEM, n=3-10 one way repeated measures ANOVA-Dunnett's t-test). Insert: Effect of CHL on 1 mM nicotine-induced peak DA release in the mPFC. *$p<0.05$, **$p<0.01$ vs nicotine alone (mean ± SEM, n=4-10 two way ANOVA- Newman-Keuls test).

Figure 2 Effect of co-infusion of 10 μM DHβE on nicotine-induced peak DA release in mPFC. *$p<0.05$ vs nicotine alone (mean ± SEM, n=5-10 two way ANOVA- Newman-Keuls test).

These data demonstrate that local nAChR within the mPFC can facilitate DA release and that the β2 containing nAChR subtype contributes to this response. (Supported by BBSRC grant BBS/B/15600).

Brown, V.J., *et al*. (2002) *Trends. Neurosci*., **25:** 340-343.
Levin, E.D., *et al*. (1998) *Psychopharmacol (Berl).*, **138:** 217-230.