α7 nicotinic acetylcholine receptors facilitate spontaneous glutamate release in the rat prefrontal cortex

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Nicotinic acetylcholine receptors (nAChR) have been implicated in processes such as attention, learning and memory. A variety of approaches have shown that nicotine can enhance glutamate release in the prefrontal cortex, an area strongly implicated in attentional processes linked to working memory (Gionni et al., 1999; Lambe et al., 2003). By monitoring release of [^{3}H]-D-aspartate from prefrontal cortex synaptosomes we have recently shown that the increase is likely to depend partly on activation of presynaptic α7 nAChR (Dickinson et al, 2008). In the present study we have examined this possibility using an electrophysiological approach.

Spontaneous excitatory postsynaptic currents (sEPSCs) mediated by AMPA receptors were recorded from neurones with pyramidal morphology in prefrontal cortical slices prepared from male Wistar rats (60-70g), using whole cell-patch clamp. These were used as a reporter of presynaptic glutamate release.

The selective α7 nAChR agonist, AR-R17779 ([(2)-spiro[1-azabicyclo[2.2.2]octane-3,59-oxazolidin]-29-one]; a gift from GSK; 10 μM) increased sEPSC frequency from 7.7±1.8 Hz to 10.7±2.6 Hz (+47±30.1 %; n=4; P<0.05, paired t-test). Choline, at a concentration (10 mM) selective for α7 nAChR, had qualitatively similar effects (n=4). Mean sEPSC frequency only increased from 6.1±1.3 Hz to 6.9±1.0 Hz, but the mean percentage increase in frequency (42.8±32.3%; P<0.05, paired t-test) was similar to that seen with AR-R17779. Mean amplitude of sEPSCs was not significantly changed by either AR-R17779 (17.0±3.5 *vs* 14.4±2.4 pA) or choline (13.3±0.6 *vs* 11.7±1.0 pA). With both drugs there was a large variation in effect, with some neurones showing little change and others more marked. Because α7 nAChR, rapidly desensitize in response to agonist activation, we also tested the effects of AR-R17779 in the presence of a positive allosteric modulator, PNU-120596, which reduces desensitization. In the presence of PNU-120596 (10 μM, n=6) the baseline frequency of sEPSCs was increased (11.0±2.9 Hz). Subsequent application of AR-R17779 further increased frequency to 15.4±3.5 Hz, an overall increase of 62.3±29.9% (P<0.05, paired t-test). Amplitude was again unaffected (14.4±0.5 *vs* 14.3±0.8 pA).

Thus, the increase in frequency of sEPSCs with no change in amplitude support the observation that α7 nAChR on presynaptic terminals facilitate spontaneous glutamate release in the prefrontal cortex (Dickinson et al, 2008). The results with PNU-120596 suggest that these receptors may be tonically activated and partially desensitized by ambient levels of ACh or choline.

We thank the BBSRC for a Vacation Scholarship for AL and a PhD Scholarship for SELC

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