Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue3abst157P.pdf

α7 Nicotinic Acetylcholine Receptors Exert Bidirectional Control Over Inhibitory And Excitatory Neurotransmission Within The Mouse Prelimbic Cortex.

Matt Udakis, Susan Wonnacott, Chris Bailey. University of Bath, Bath, UK

We have previously shown that PNU-120596 (PNU-1), a positive allosteric modulator (PAM) at α7 nicotinic acetylcholine receptors (α7 nAChRs) enhanced glutamatergic input onto layer V pyramidal neurons in the mouse prelimbic cortex brain slice. In contrast, a more pronounced α7 nAChR activation with co-application of the PAM and the selective α7 nAChR agonist PNU-282987 (PNU-2) enhanced GABAergic input onto the same neurons (1). We hypothesised that α7 nAChRs are able to regulate neurotransmission within the prelimbic cortex by acting on two distinct neurotransmitter systems independently.

To test this hypothesis we conducted a variety of brain slice electrophysiology experiments in 5 week old C57BL/6 naïve mice in accordance to the Animals (Scientific Procedures) Act, 1986, UK. Whole cell voltage-clamp recordings of Layer V pyramidal neurons (2) were used to record spontaneous and miniature GABA (sIPSCs and mIPSCs) and glutamate (sEPSCs and mEPSCs) currents. mIPSCs and mEPSCs were recorded in the presence of 1 μM tetrodotoxin. Evoked EPSCs were also recorded via bipolar stimulation of distal dendrites 50 - 100 μm from the recorded cell.

The α7 nAChR PAM, PNU-1 (10 μM), increased the frequency of mEPSCs with no change in the amplitude.. This implicates presynaptic α7 nAChRs that enhance glutamate release. The selective α7 nAChR antagonist methyllycaconitine (MLA; 100 nM) reduced the amplitude of evoked EPSCs by 19±9% ($n = 4$, $P < 0.05$; paired t-test). Furthermore, MLA also led to a 5 ± 1% increase in the paired pulse ratio ($n = 5$, $P < 0.05$; paired t-test). Together these results suggest that presynaptic α7 nAChRs are activated by tonically released ACh to alter the probability of glutamate release.

Consistent with previous findings (1), co-application of PNU-1 (10 μM) with the selective α7 nAChR agonist PNU-2 (300 nM) increased the frequency of sIPSCs compared to control and this was unaffected by the presence of the AMPAR antagonist DNQX (10 μM). However, co-application of PNU-1 and PNU-2 did not alter the frequency or amplitude. These results are consistent with a distinct action of α7 nAChRs on GABA release via α7 nAChRs located on inhibitory interneuron bodies rather than terminals that are not accessed by tonic ACh but require addition of agonist.

In summary α7 nAChRs can modulate the activity of the prelimbic cortex via their expression on glutamate terminals and inhibitory interneurons, enabling them to regulate excitatory and inhibitory signalling respectively - a process that may have implications for network control of the prelimbic cortex.

Table 1. – Spontaneous and miniature EPSC and IPSC frequency and amplitude data.

Control vs PNU-1		**Control vs PNU-1 + PNU-2 (in DNQX)**		
mEPSC		sIPSC	mIPSC	
Freq. (events min^{-1})	Amplitude (pA)	Freq. (events min^{-1})		Amplitude (pA)
405 ± 56 vs 477 ± 68	8.3 ± 0.4 vs 7.9 ± 0.3	778 ± 176 vs 1080 ± 254	992 ± 99 vs 950 ± 82	19.2 ± 2 vs 19.7 ± 2
n = 11 ; P < 0.05	n=11 ; P > 0.05	n = 6 ; P < 0.001	n = 6 ; P > 0.05	n = 5 ; P > 0.05

all statistical analysis in table performed via Kolmogorov-Smirnov test

(1) Udakis M et al. (2013). http://www.pa2online.org/abstracts/vol11issue3abst072p.pdf.

(2) Poorthuis RB et al. (2012). *Cerebral Cortex* **23**:148–161.