Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue3abst233P.pdf

α7 Nicotinic Acetylcholine Receptors Regulate Glutamate Release within the Medial Prefrontal Cortex of the Mouse

α7 nicotinic acetylcholine receptors (nAChRs) are implicated in multiple brain disorders such as Alzheimer's disease, schizophrenia, addiction and ADHD. We have previously shown that α7 nicotinic acetylcholine receptors (nAChRs) regulate the excitation of pyramidal neurons in the prelimbic region of the mouse medial prefrontal cortex (mPFC) (1). The mPFC receives afferent glutamatergic input from numerous brain regions, including the ventral hippocampus, thalamus and amygdala. The aim of this study was to elucidate which afferent inputs express functional α7nAChRs.

Acute brain slices were prepared from male C57BL/6 mice. Whole-cell voltage-clamp recordings were made from Layer V pyramidal neurons in the mPFC (1). By preparing mPFC brainslices containing the afferent projections from the ventral hippocampus (2), we were able to selectively evoke and record hippocampus-mPFC excitatory postsynaptic currents (EPSCs). We observed no significant alteration in the EPSC amplitude in response to sequential bath application of 10 μM PNU-120596(an α7 nAChR positive allosteric modulator (PAM)) and co-application of α7 PAM and 0.3 μM PNU-282987 (α7nAChR agonist). Normalised evoked EPSC amplitudes (n = 4);Control: 98 ± 3%, PAM: 89± 9%, PAM &agonist 82 ± 22%. One-way ANOVA with Tukey's multiple comparison test showed no significant differences. These data provide no evidence forα7nAChRsresiding on hippocampal excitatory inputs to the mPFC.

We have previously shown that application of the α7 nAChR PAM alone caused a significant increase in the frequency of spontaneous excitatory postsynaptic currents. These events are likely to derive from a combination of afferent inputs (eg. glutamatergic neurons deriving from the ventral hippocampus, thalamus, amygdala). Glutamatergic afferents residing from the thalamus, but not from other brain regions, largely express μ-opioid receptors (3). Thisenabled us to selectively inhibit thalamic glutamate terminals with the μ-opioid agonist DAMGO(3). In the presence of 3 μM DAMGO, application of the α7 nAChR PAM alone no longer induced a significant increase in the frequency of spontaneous excitatory postsynaptic currents (DAMGO: 7.2± 0.9, DAMGO & PAM: 7.2 ± 1.0 Hz. n = 6. P > 0.05, Kolmogorov Smirnov test). This initial evidence suggests α7 nAChRs may reside on thalamic terminals.

To investigate this further we injected an AAV viral vector containing channel rhodopsin into the thalamus of C57BL/6 mice. After 6 weeks expression, we could selectively evoke thalamic glutamate release within the mPFC brain slice using blue light. Co-application of10 μM α7 PAM with 0.3 μM α7 agonist significantly enhanced the levels of light-evoked thalamo-cortical glutamate EPSCs (Normalised amplitudes; Control: 100 ± 1%, α7 PAM + α7 agonist: 117 ± 3%. P= 0.0072. n = 4. ANOVA with Dunnett's multiple comparison test), providing further evidence that thalamo-cortical glutamate release is regulated byα7nAChRs. Optogenetics studies are ongoingto investigate additional loci for α7nAChRswith an aim at further elucidating how these receptors modulate excitatory input to the mPFC.

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

(2) Parent MA et al. (2009) Cereb Cortex 20: 393-403.

(3) Lambe EK et al. (2003) Neuropsychopharmacology 28: 216-225