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Subtype-selective nicotinic acetylcholine receptor agonists can improve cognitive flexibility in an attentional set shifting task

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ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) are considered to be viable targets to enhance cognition in patients diagnosed with schizophrenia. Activation of nAChRs with selective nicotinic receptor agonists may provide effective means to pharmacologically treat cognitive deficits observed in schizophrenia. Cognitive flexibility is one aspect of cognition, which can be assessed in a rodent model of the attentional set-shifting task (ASST). The aim of the present study was two-fold, firstly, to evaluate the efficacy of a series of subtype selective nAChR agonists, such as those that target α7 and α4β2 nAChR subtypes in non-compromised rodents. Secondly, nicotine as a prototypic agonist was evaluated for its effects to restore attentional deficits produced by sub-chronic ketamine exposure in the ASST. Male hooded Lister rats underwent habituation, consisting of a simple odour and medium discrimination with subsequent assessment 24 h later. In experimentally naïve rats, α7 subtype selective agonists, compound-A and SSR180711 along with PNU-120596, an α7 positive allosteric modulator (PAM), were compared against the β2* selective agonist, 5IA-85380. All compounds except for PNU-120596 were observed to significantly improve extra-dimensional (ED) shift performance, nicotine, 5IA-85380 and SSR180711 further enhanced the final reversal (REV3) stage of the task. In another experiment, sub-chronic ketamine treatment produced robust deficits during the ED and the REV3 stages of the discriminations; rodents required significantly more trials to reach criterion during these discriminations. These deficits were attenuated in rodents treated acutely with nicotine (0.1 mg/kg SC) 10 min prior to the ED shift. These results highlight the potential utility of targeting nAChRs to enhance cognitive flexibility, particularly the α7 and β2* receptor subtypes. The improvement with nicotine was much greater in rodents that were impaired following the sub-chronic ketamine exposure suggesting a greater therapeutic opportunity to target nicotinic receptors for patients diagnosed with schizophrenia.

1. Introduction

Nicotine is the major exogenous compound contained in tobacco products that has been shown to enhance cognition through activation of nAChRs, with reports highlighting the significance of nAChRs within the prefrontal cortex (PFC) (Livingstone et al., 2010; Vidal, 1994), a brain region that has been associated with cognitive flexibility (Dalley et al., 2004; Gil et al., 1997). The therapeutic potential of targeting nAChRs for cognitive decline is not restricted to deficits associated with schizophrenia (Palmer et al., 1997), since this symptom is also apparent in other neuropsychiatric disease states such as Alzheimer's disease, affective disorders and ADHD (Sacco et al., 2004). The notable observation of heavy tobacco use amongst patients with schizophrenia (Chapman et al., 2009; Miyata, 2008; Tidey et al., 2005) highlights the notion of self-medication to remediate the cognitive deficits. Studies have shown that acute nicotine exposure can improve cognition, independent of smoking in patients diagnosed with schizophrenia (AhnAllen et al., 2008; Barr et al., 2008; Sacco et al., 2005). With the limited array of medications to enhance cognition, there has been a growing interest in targeting nAChRs, particularly those that activate combinations of nicotinic subunits (α2-10, β2-4), with the most predominant isoforms α4β2 and α7 subtypes which are implicated in attentional deficits (Freedman et al., 1997). The α4β2 and α7 nAChR subtypes are expressed centrally and are located on both pre- and post-synaptic membranes (Gotti and Clementi, 2004).

Polymorphisms of the α7 nAChR gene (CHRNA7) are one of the

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susceptibility genes for schizophrenia that is associated with P50 gating deficits and an increased risk of developing tobacco dependence (De Luca et al., 2004; Freedman et al., 1997; Stefansson et al., 2008). Patients diagnosed with schizophrenia have reduced level of CHRNA7 protein expression (Mexal et al., 2010) and elevated levels of autoantibodies against the α7 receptor subunit (Chandley et al., 2009). Similarly, post-mortem studies in patients diagnosed with schizophrenia report reduced hippocampal and frontal cortex expression of the α7 nAChR (Freedman et al., 1995; Guan et al., 1999). There is relatively less published on the α4β2 nAChR subtype which is ubiquitously expressed in these frontal cortical areas along with high levels expressed in the thalamus and the ventral tegmental area (VTA) (Ding et al., 1996). Similarly, the α7 nAChR subtype is also found in the PFC, which can modulate various neurotransmitters such as: glutamate, GABA and dopamine (Alkondon et al., 1997; Livingstone et al., 2010).

Using behavioural models of cognition, we have previously reported on the effects of nicotine and related nicotinic agonists in a non-spatial working memory capacity task in non-compromised rodents; acute administration of nicotine (0.05 and 0.1 mg/kg SC) or the selective α7 agonist, compound A (10 mg/kg IP) or the α4β2 agonist, metanicotine (0.1 mg/kg SC), all significantly improved performance above baseline performance levels (Rushforth et al., 2010). Subsequently, in studies which involved treating rodents with a sub-chronic ketamine regimen which impaired performance in the working memory capacity task, nicotine was shown to robustly improve performance in both vehicle and ketamine-treated rats (Rushforth et al., 2011). However, in contrast, these ketamine-induced deficits were not reversed with clozapine (1–10 mg/kg) or the mGlu2/3 agonist LY404039 (0.3–10 mg/kg) (Rushforth et al., 2011).

Recently, we reported on nicotine enhancing another cognitive domain in rats. In the rodent version of the ASST, acute injections of nicotine enhanced set-shifting performance within the intra-dimensional (ID) and the extradimensional (ED) shifts in normal rats, an effect also observed in rats treated sub-chronically with nicotine (0.2 mg/kg daily for three consecutive days prior to testing) (Allison and Shoaib, 2013). These improvements on cognitive flexibility were dose-dependent suggesting nAChRs as potential targets for enhancing performance in the attentional set-shifting task.

Several nicotinic ligands have been developed to selectively target the different nAChR subtypes. Two of the early α7 agonists are GTS-21 and AR-R17779. Despite exhibiting some cognitive-enhancing effects in passive and active avoidance tasks and in spatial working memory tasks (Arendash et al., 1995; Meyer et al., 1998; Kem, 2000), these compounds were not deemed to be selective and or exhibited poor CNS penetration. Compound A is a selective α7 agonist (Cilia et al., 2005) that can increase extracellular levels of dopamine in the medial region of PFC (Livingstone et al., 2010). The selective α7 nAChR agonist SSR180711 (Biton et al., 2007) has been shown to enhance episodic memory in the object recognition task in rats and mice (Pichat et al., 2007) and also restore MK801-induced deficits in retention of episodic and spatial working memory (Pichat et al., 2007). Very few studies have evaluated α7 agonists on cognitive flexibility in rodents. The α7 positive allosteric modulator PNU-120596 has been reported to restore deficits on attentional shifts following sub-chronic phencyclidine (PCP) treatment in rats (McLean et al., 2012). With regards to the α4β2 nAChR subtype, no studies have systematically evaluated specific α4β2 agonists in models of attention set-shifting. The commercially available agonist, 5IA-85380 developed as a SPECT ligand to assess β2* nAChR subunits, has not been evaluated for cognitive-enhancing properties in rodents.

Extensive research has highlighted the link between N–methyl-D-aspartate (NMDA) dysfunction and cognitive impairment observed in schizophrenia (Gilmour et al., 2012). From a preclinical perspective, cognitive deficits associated with schizophrenia can be reliably modelled in rodents by treating with non-competitive antagonists of the N–methyl-D-aspartate receptor (NMDA-R) that produce behavioural symptomatology associated with schizophrenia in humans (Jentsch and Roth, 1999; Krystal et al., 1994). Typically, studies utilise sub-chronic exposure of PCP, administered to rats repeatedly to induce deficits on various cognitive domains (Arnt et al., 2010; Goetghebeur and Dias, 2009; Rodefer et al., 2005, 2008). The dissociative anaesthetic, ketamine shares similar pharmacological activity and can also induce cognitive dysfunction and augment psychotic symptomatology in healthy volunteers and patients diagnosed with schizophrenia, respectively (Krystal et al., 1994; Lahti et al., 1999). Buccafusco and Terry (2009) administered sub-sedative doses of ketamine to monkeys in a computer-assisted response task, resulting in reduced accuracy. These deficits were fully reversed by a α7 nAChR partial agonist (Buccafusco and Terry, 2009). Finally, as discussed above, we have reported on a chronic ketamine exposure that impaired performance for a prolonged period within a memory capacity of working memory task in rats (Rushforth et al., 2011).

The aim of this study was twofold: firstly to distinguish which nAChR subtype selective agonists selective for the α4β2 and α7 nAChR subtypes can produce nicotine-like improvements in the ASST as reported by Allison and Shoaib (2013). Secondly, the effects of nicotine will be examined in rodents treated with a five-day sub-chronic ketamine dosing regimen. It is predicted that ketamine exposure will produce a similar profile of impairment as previously reported for PCP (Neill et al., 2010) and that acute nicotine administration prior to the ED shift will produce a greater enhancing effect in rodents to switch between the perceptual dimensions.

2. Method

2.1. Animals

Male Lister hooded rats (Harlan UK, Bicester, Oxfordshire) (n = 172) weighing between 260 and 320 g at the time of testing were housed in pairs in (28 cm × 45 cm × 13 cm) Perspex cages (North Kent plastic cage company "RB3"). In temperature (21 ± 1 °C) and light controlled (12hr cycle) rooms, behavioural tests took place during the light phase from 0700hr until 1900hr. The rats had access to drinking water at all times but food was restricted to maintain their body weight at ≥85% of their free-feeding body weight with daily monitoring in respect to a standard growth curve. The Animals (Scientific Procedures) Act 1986 and associated local guidelines were adhered to throughout the process.

2.2. Apparatus

The testing equipment was based on a modified plastic cage (*approx.* 40 cm × 73 cm × 19 cm), with 1/3 being split into two compartments (*by Plexiglas panels*), which housed the ceramic bowls. A removable Perspex divider separated these sections from the rest of the box so access to both bowls could be controlled during testing. A smaller Perspex divider was used when required to block access to either of the bowls individually, for example when an error was recorded (see below).

2.3. Habituation

The habituation and testing phases were similar to the versions