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Combined α7 nicotinic acetylcholine receptor agonism and partial serotonin transporter inhibition produce antidepressant-like effects in the mouse forced swim and tail suspension tests: A comparison of SSR180711 and PNU-282987

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ABSTRACT

Emerging evidence points to an involvement of nicotinic acetylcholine receptors (nAChRs) in major depression. Nicotine improves symptoms of depression in humans and shows antidepressant-like effects in rodents. Monoamine release is facilitated by nAChR stimulation, and nicotine-evoked serotonin (5-HT) release has been shown to depend on α7 nAChR activation. The α7 nAChR agonist PNU-282987 shows no antidepressant-like activity when tested alone in the mouse forced swim (mFST) or tail suspension tests (mTST). However, in combination with a sub-active dose of the selective 5-HT reuptake inhibitor citalopram, inducing ~50% 5-HT reuptake inhibition, PNU-282987 has shown marked antidepressant-like effects in the mFST. SSR180711 is a recently described α7 nAChR agonist that has shown antidepressant-like activity in the rat forced swim test. To address the possibility that 5-HT reuptake inhibition contributes to the antidepressant-like profile of SSR180711, we compared the behavioural and biochemical profiles of PNU-282987 and SSR180711. In the mFST and mTST, SSR180711 (3–30 mg/kg, s.c.) showed dose-dependent antidepressant-like activity, while PNU-282987 (3–30 mg/kg, s.c.) showed no significant effect. The ED_{50} to displace [^{3}H]α-bungarotoxin binding was 1.7 and 5.5 mg/kg for SSR180711 and PNU-282987, respectively, suggesting that both compounds produce near-maximal α7 nAChR occupancy at the highest dose. While PNU-282987 did not affect *ex vivo* [^{3}H]5-HT uptake, SSR180711 inhibited [^{3}H]5-HT uptake with an ED_{50} of 30 mg/kg. This degree of inhibition is similar to that observed with a citalopram dose of ~2.4 mg/kg, a dose that is normally not active in the mFST or mTST. This suggests that the antidepressant-like activity of SSR180711 may involve partial 5-HT reuptake inhibition. SSR180711 therefore represents a compound displaying the synergistic effect of α7 nAChR agonism combined with partial 5-HT reuptake inhibition previously described. The addition of α7 nAChR agonism to classical monoamine-based mechanisms may represent a novel option for the improved treatment of major depression.

1. Introduction

Over the past few decades, nicotinic acetylcholine receptors (nAChRs) have been intensively studied as potential targets for novel psychopharmacological treatments. Given the well-established beneficial effects of nicotine on cognitive performance (Levin et al., 2006; Newhouse et al., 2004), the predominant focus has traditionally been directed at cognitive deficits associated with neuropsychiatric disorders. More recently, clinical and preclinical evidence has linked nAChRs to major depressive disorder (Mineur and Picciotto, 2010; Philip et al., 2010). Nicotine improves mood in non-smoking patients with major depression (McClernon et al., 2006), and both nicotine and other nAChR agonists show activity in various behavioural assays predictive of antidepressant properties, including the rat forced swim test (rFST) (Djuric et al., 1999; Nowakowska et al., 2006; Tizabi et al., 1999, 2009; Vazquez-Palacios et al., 2005), the mouse forced swim test (mFST) (Andreasen and Redrobe, 2009a; Caldarone et al., 2011; Gatto et al., 2004), the rat learned helplessness paradigm (Ferguson et al., 2000), and the chronic mild stress model of depression (Andreasen et al., 2011; Pichat et al., 2007), an animal model thought to display predictive, face and construct validity (Willner, 2005).

Nicotine increases the firing rate of serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN), the major source of forebrain serotonergic innervation (Mihailescu et al., 1998, 2002), and increases 5-HT release in several forebrain regions (Kenny et al., 2000; Reuben and Clarke, 2000; Ribeiro et al., 1993; Tucci et al., 2003). 5-HT neurons possess functional postsynaptic nAChRs of both the high-affinity α4β2 and the low-affinity α7 nAChR subtypes (Aznar et al., 2005;

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Galindo-Charles et al., 2008), and there is evidence to suggest that both subtypes mediate nicotine-evoked 5-HT release (Ma et al., 2005; Reuben and Clarke, 2000; Tucci et al., 2003). For instance, it has been demonstrated that nicotine-evoked 5-HT release in the hippocampus depends on α7 nAChR activation (Tucci et al., 2003). It is therefore feasible that α7 nAChR-mediated cholinergic–serotonergic interaction is involved in the antidepressant properties of nicotine.

The mFST and mouse tail suspension test (mTST) are two tests often employed to assess potential antidepressant effects. In these tests, NMRI mice do not respond to nicotine, the α4β2-selective nAChR agonist TC-2403, or the α7-selective nAChR PNU-282987 (Andreasen et al., 2009; Andreasen and Redrobe, 2009a, 2009b). This suggests that α7 or α4β2 nAChR agonism alone is insufficient to produce antidepressant-like effects in NMRI mice. Nonetheless, using this mouse strain, we found that the effects of sub-active doses of the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram were rendered active upon co-administration of nicotine (Andreasen and Redrobe, 2009b), as well as with the α4β2-selective nAChR agonist NS3956, or the α7-selective nAChR agonist PNU-282987 (Andreasen et al., 2010).

SSR180711 is a recently described α7 nAChR agonist that has shown antidepressant-like activity in the rat forced swim test (Pichat et al., 2007). This is in contrast to the lack of effect of the selective α7 nAChR agonist PNU-282987 in the mFST (Andreasen et al., 2009, 2010). While these apparently contradictory findings could result from species differences, an alternative possibility is that other mechanisms of SSR180711, not related to α7 nAChR agonism, contribute to the antidepressant-like profile of this compound. Our previous finding that PNU-282987 enhanced the effects of citalopram in the mFST points to a potential involvement of the serotonin transporter (SERT) in mediating the antidepressant-like effect of SSR180711.

Thus, the present study was undertaken to compare the effects of SSR180711 and PNU-282987 in the mFST and mTST, and relate the behavioural findings to the α7 nAChR and SERT binding profiles of these two α7 agonists.

2. Material and methods

2.1. Animals

Female NMRI mice (22–26 g) obtained from Taconic M&B (Ry, Denmark) were used for all experiments and were 8–9 weeks of age at the time of testing. After arrival, mice were allowed a minimum of 7 days acclimatisation in Macrolon III cages (20×40×18 cm) with 8 mice/cage. All cages were enclosed within a Scantainer (Scanbur A/S, DK). Female mice were used because male mice often display vigorous fighting and occasional killing of each other. Besides ethical concerns, such intense stress may considerably confound results obtained with behavioural tests related to affective disorders. Females were groups housed and isolated from male mice. This is known to suppress estrus, *i.e.* the normal 4–5 day cycling in female mice is prolonged, and absence of male pheromones results in a state of anestrus (Whitten effect) (Ma et al., 1999; University of California Breeding Information, 2011). Moreover, under these conditions female mice would be expected to cycle synchronously, given that cycling is still present (Lee–Boot effect) (Koyama, 2004). Food and water were available *ad libitum* on a 12/12 h light/dark cycle with lights on at 6 am. Experiments were performed between 9:00 am and 16:00 pm in temperature and humidity-regulated rooms (22–24 °C, relative humidity: 60–70%). All testing procedures were in accordance with "Principles of Laboratory Animal Care" (NIH publication No. 85-23, revised 1985) and the Danish Animal Experimentation Act, and all efforts were made to minimise animal suffering.

2.2. Drugs and treatment

PNU-282987 (N-(3R)-1-azabicyclo[2.2.2]oct-3-yl-4-chlorobenzamide fumarate and SSR180711 (4-bromophenyl 1,4diazabicyclo(3.2.2) nonane-4-carboxylate, monohydrochloride) were synthesized at NeuroSearch A/S. [^{3}H]α-bungarotoxin (60 Ci/mmol) was purchased from GE Healthcare UK Limited (Little Chalfont, UK). [^{3}H]5-HT (21 Ci/mmol) was purchased from PerkinElmer Life and Analytical Sciences (Boston, MA). Citalopram was purchased from Actavis (Gentofte, Denmark). All other chemicals were purchased from regular commercial sources and were of the purest grade available. For behavioural studies, PNU-282987 (3–30 mg/kg) and SSR180711 (3–30 mg/kg) were administered 30 min prior to testing. Drugs were dissolved in saline and administered subcutaneously in an injection volume of 10 ml/kg. Doses are expressed as the free base of the drug.

2.3. Ex vivo binding studies

Groups of three female NMRI mice were injected s.c. (SSR190711 and PNU-282987) or i.p. (citalopram) with drug solutions or vehicle. Three to four doses ranging from 0.3 to 40 mg/kg were tested for determination of ED_{50} values. Thirty minutes after drug administration mice were killed by decapitation and cerebral cortices (for SERT studies)/hippocampi (for α7 studies) were rapidly dissected on ice and the tissue weighed. Preparations were performed at 0–4 °C unless otherwise indicated. Groups of vehicle-treated mice served as controls for estimation of total and non-specific binding/uptake.

2.3.1. SERT studies

The cerebral cortex from the individual animals was homogenised for 5–10 s in 100 volumes of ice-cold 0.32 M sucrose containing 1 mM pargyline using a motor driven Teflon pestle in a glass homogenising vessel. The homogenates were centrifuged at 1000×*g* for 10 min, and the resulting supernatants were diluted (400 ml/g of original tissue) in oxygenated (equilibrated with an atmosphere of 96% O2: 4% CO_2 for at least 20 min) Krebs–Ringer incubation buffer (containing 122 mM NaCl, 0.16 mM EDTA, 4.8 mM KCl, 12.7 mM Na_2HPO_4, 3.0 mM NaH_2PO_4, 1.2 mM $MgSO_4$, 1 mM $CaCl_2$, 10 mM glucose and 1 mM ascorbic acid; pH = 7.2), and used for uptake assays. The assay conditions for *in vitro* 5-HT uptake was as described previously (Munro et al., 2008). In brief, the assay was performed at 5 nM [^{3}H]5-HT in a total volume of 2.1 ml, mixed and incubated for 30 min at 37 °C in triplicate. Non-specific uptake was determined in the presence of 1 μM Citalopram.

2.3.2. α7 studies

Each pair of hippocampi was homogenised for 10 s in 75 volumes (75 ml/g of original tissue) of ice-cold 50 mM Tris, HCl (pH 7.4) containing 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2.5 mM CaCl2 and 0.01% BSA using an Ultra-Turrax homogeniser, and used for binding assays. The remaining *in vitro* procedure was performed as published by Gopalakrishnan et al. (1995). In brief, the assay was performed at 1 nM [^{3}H]α-bungarotoxin ([^{3}H]α-BgTx) in a final volume of 0.55 ml, mixed and incubated for 2 h at 37 °C in triplicate. Non-specific binding was determined in the presence of 1 mM (−)-nicotine.

Incubations were terminated by rapid vacuum filtration, and the amount of radioactivity on the filters was determined by conventional liquid scintillation counting.

2.4. Behavioural testing

2.4.1. Forced swim test

Mice (n = 8–10) were individually placed in a beaker (16 cm in diameter) filled with 20 cm water maintained at 23.5–24.5 °C. Total swim distance during the 6-min test period was automatically recorded by a camera mounted above the cylinders and stored on a

computer equipped with the relevant software (Viewpoint, Viewpoint Life Sciences, France).

2.4.2. Tail suspension test

Mice (n = 7–9) were suspended by the tail with adhesive tape placed ~1 cm from the tip of the tail. Immobility time during the 6 min period was recorded with an automated electromechanical strain gauge device and stored on a computer equipped with the relevant software (Med Associates Inc., Georgia, USA).

2.4.3. Locomotor activity

Locomotor activity experiments were performed to rule out non-specific stimulant effects of treatment. Mice (n = 7) were placed individually in transparent cages (30×20×25 cm) for 30 min. The activity chambers were equipped with infrared sensors (6×2) arranged along the bottom of each wall of the arena (TSE Systems, Bad Homburg, Germany). Locomotor activity was monitored automatically in the chambers and was measured as the interruption of two consecutive infrared sensors. Interruptions of infrared sensor pairs was detected by a control unit and registered by a computer equipped with the relevant software (ActiMot, TSE Systems, Bad Homburg, Germany).

2.5. Data analysis

For each behavioural test, the effects of PNU-282987 and SSR180711 were analysed by a one-way analysis of variance (ANOVA) followed by Planned Comparisons on the predicted means. To ensure variance homogeneity, which is required before ANOVA can be performed, data were log-transformed before statistical analysis where appropriate; all graphs display observed means with SEMs on the original scale. Of the 6-min mFST data, the first minute was omitted before data analysis. ED_{50} values in *ex vivo* studies were determined from dose–response curves based on the equation $B = 100 - (100 \times D/(ED_{50} + D))$, where B is the binding/uptake in percent of total specific binding/uptake; and D the dose of test compound.

3. Results

3.1. Ex vivo binding studies

Results from the *ex vivo* binding studies are shown in Table 1. SSR180711 and PNU-282987 inhibited [^{3}H]α-BgTx binding with ED_{50} values of 1.7 and 5.5 mg/kg respectively. While PNU-282987 did not inhibit [^{3}H]5-HT uptake at the doses tested (up to 40 mg/kg), SSR180711 inhibited [^{3}H]5-HT uptake with an ED_{50} value of 30 mg/kg. In comparison the ED_{50} of citalopram to inhibit [^{3}H]5-HT uptake was 2.4 mg/kg.

3.2. Behavioural testing

3.2.1. Forced swim test

Fig. 1 shows the effect of PNU-282987 (a) and SSR180711 (b) on swim distance in the mFST. PNU-282987 did not significantly alter swim distance at the doses tested ($F_{3,25} = 0.46$; $p = 0.716$). SSR180711 dose-dependently increased swim distance ($F_{3,35} = 6.78$; $p < 0.001$), with Planned Comparisons showing a significant increase at 10 mg/kg ($p = 0.047$) and 30 mg/kg ($p < 0.001$).

3.2.2. Tail suspension test

Fig. 2 shows the effect of PNU-282987 (a) and SSR180711 (b) on immobility time in the mTST. PNU-282987 did not significantly alter immobility time at the doses tested ($F_{3,27} = 2.25$; $p = 0.105$). SSR180711 decreased immobility ($F_{3,33} = 3.21$; $p = 0.035$), with Planned Comparisons showing a significant decrease at 30 mg/kg ($p = 0.017$).

3.2.3. Locomotor activity

Fig. 3 shows the effect of PNU-282987 (a) and SSR180711 (b) on locomotor activity (30 min). PNU-282987 did not significantly alter distance travelled at the doses tested ($F_{3,23} = 1.31$; $p = 0.293$). SSR180711 decreased total distance ($F_{3,25} = 16.42$; $p < 0.001$), with Planned Comparisons showing a significant decrease at 30 mg/kg ($p < 0.001$).

Table 1
Assessment of α7 nAChR occupancy using *ex vivo* [^{3}H]α-BgTx binding (hippocampus) and SERT occupancy using *ex vivo* [^{3}H]5-HT uptake (cortex). Binding and uptake assays were performed as described under Materials and methods. All compounds were administered 30 min before start of *ex vivo* experiments. Tissue preparations are based on tissue weight. Data are given as mg/kg free base, the range representing results from two independent experiments. NA: not applicable.

Compound	*Ex vivo* [^{3}H]α-BgTx ED_{50} (mg/kg)	*Ex vivo* [^{3}H]5-HT ED_{50} (mg/kg)	Route
SSR180711	1.7 (1.3; 2.1)	30 (26; 36)	s.c.
PNU-282987	5.5 (4.4; 6.6)	>40	s.c.
Citalopram	NA	2.4 (2.0; 2.9)	i.p.

4. Discussion

This study compared the potential antidepressant-like effects of the two different α7 nAChR agonists, PNU-282987 and SSR180711. PNU-282987 was devoid of antidepressant-like activity, confirming previous studies (Andreasen et al., 2009; 2010). By contrast, SSR180711 showed antidepressant-like effects in both the mFST and mTST without locomotor-stimulant effect. PNU-282987 and SSR180711 have been shown to have similar potency and efficacy at human α7 nAChRs expressed in oocytes (Redrobe et al., 2009). The *ex vivo* [^{3}H]α-BgTx ED_{50} values found here (Table 1) are in line with those reported by Redrobe et al. (2009). Based on these values, both compounds are likely to produce full occupancy of α7 nAChRs at the highest dose (30 mg/kg). A notable difference, however, is that PNU-282987 showed no detectable [^{3}H]5-HT uptake inhibition, while SSR180711 inhibited [^{3}H]5-HT uptake with an ED_{50} of ~30 mg/kg. This degree of inhibition is similar to that observed with ~2.4 mg/kg citalopram.

Thus, at the 30 mg/kg dose of SSR180711, which produced marked antidepressant-like effect, a maximal or near-maximal α7 nAChR occupancy, and approximately half-maximal SERT inhibition, is obtained. Interestingly, a previous study from our laboratory demonstrated that PNU-282987 strongly enhanced the effect of citalopram in the mFST (Andreasen et al., 2009). This enhancement by PNU282987 of citalopram's effects in the mFST was obtained with 30 mg/kg PNU-282987, a dose giving full occupancy of α7 nAChRs (Redrobe et al., 2009), and 3 mg/kg citalopram giving partial (~50%) SERT inhibition. In our hands, doses of citalopram producing 50% SERT inhibition (~3 mg/kg citalopram) are too low to produce antidepressant-like effects in the mFST and mTST (Andreasen et al., 2009; 2010; Andreasen and Redrobe, 2009b). Also, α7 agonism alone seems insufficient to produce antidepressant-like effects. However, SSR180711 represents the concept of α7 nAChR agonism combined with partial SERT inhibition previously proposed (Andreasen et al., 2010), thus resembling the combination of PNU-282987 and citalopram. This concept may provide new opportunities for more effective alleviation of depressive symptoms. The mFST and mTST are considered to be predictive of antidepressant efficacy, but in contrast to the chronic mild stress model of depression they lack face and construct validity. The present data support a previous report that SSR180711 showed effect in the mouse chronic mild stress model (Pichat et al., 2007), and using this model to compare SSR180711 and PNU-282987, or to study the combination of PNU-282987 and an SSRI, would strengthen the hypothesis that α7 agonism enhances the effects of SERT inhibition.

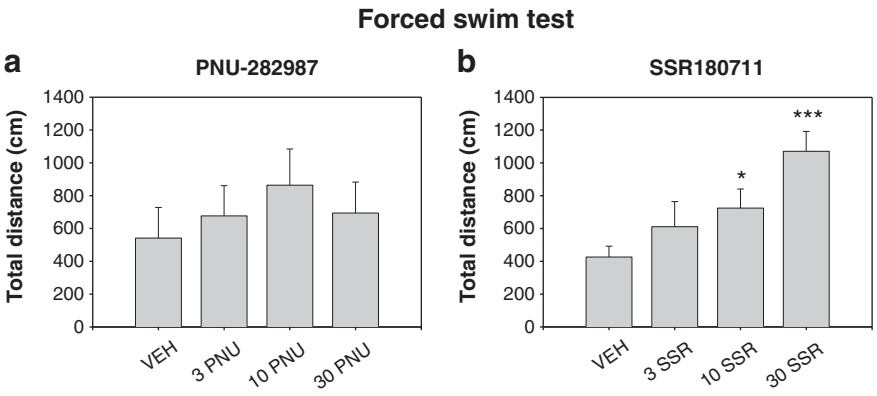

Fig. 1. Effect of PNU-282987 (a) and SSR1810711 (b) on swim distance in the mFST. PNU-282987 did not significantly affect swim distance. SSR180711 significantly increased swim distance at 10 and 30 mg/kg. */*** = significantly different from VEH ($p<0.05/0.001$). Data are expressed as means + SEMs.

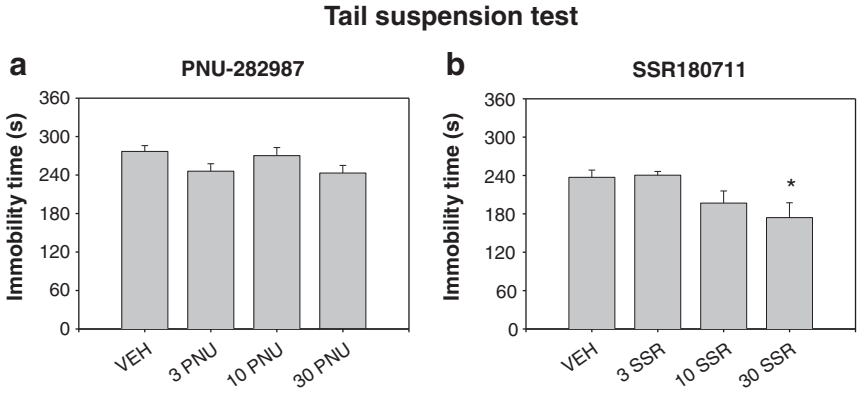

Fig. 2. Effect of PNU-282987 (a) and SSR1810711 (b) on immobility time in the mTST. PNU-282987 did not significantly affect immobility time. 30 mg/kg SSR180711 significantly decreased immobility time. * = significantly different from VEH ($p<0.05$). Data are expressed as means + SEMs.

It should be noted that the SSR180711 doses required to induce antidepressant-like effects in the present study (10–30 mg/kg) are higher than those reported by Pichat et al. (2007) to decrease immobility in the rat forced swim test (1–10 mg/kg) following acute administration. An important caveat when comparing effective doses in rats and mice is pharmacokinetic factors. For instance, the half-life of nicotine is 6–8 min in mice (Petersen et al., 1984), and ~1 h in rats (Hwa Jung et al., 2001). Accordingly, mice are generally less sensitive to nicotine's behavioural effects than are rats (Matta et al., 2007). Moreover, nAChR agonists may show differential effects in rats and mice. Thus, nicotine has been shown repeatedly to induce antidepressant-like effects in rats (*e.g.* Djuric et al., 1999; Nowakowska et al., 2006; Tizabi et al., 1999, 2009; Vazquez-Palacios et al., 2005; Ferguson et al., 2000), while only few studies have confirmed such effects in mice (but see Andreasen and Redrobe, 2009a). Likewise, the apparent discrepancy between the minimum effective doses found in the present study and in the study by Pichat et al., respectively, might be attributable to species differences in behavioural response to manipulations of the cholinergic and/or serotonergic systems. Nevertheless, Pichat et al. (2007) did

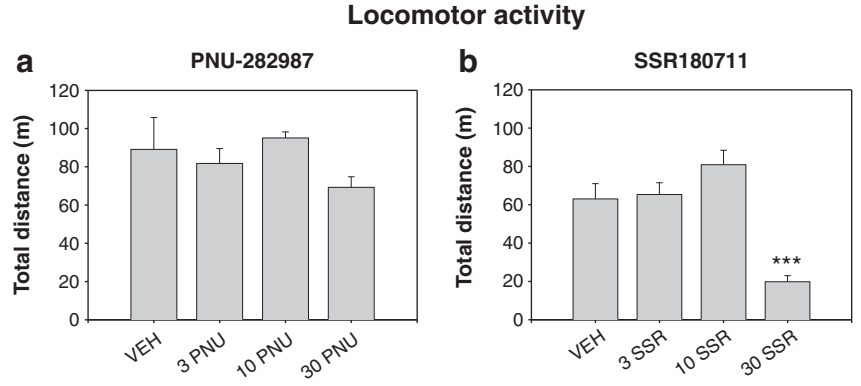

Fig. 3. Effect of PNU-282987 (a) and SSR1810711 (b) on distance travelled in the locomotor activity paradigm. PNU-282987 did not significantly affect locomotor distance. 30 mg/kg SSR180711 significantly decreased locomotor distance. *** = significantly different from VEH ($p<0.001$). Data are expressed as means + SEMs.

demonstrate a reversal of the physical degradation induced by the application of a chronic mild stress protocol in mice, following 3-week administration of SSR180711 (10 mg/kg). However, the differences in treatment regime together with the absence of drug exposure analysis in both studies may preclude meaningful comparison.

Locomotor-stimulation was not observed at the SSR180711 doses tested, indicating that the effects of SSR180711 in the mFST and mTST were not driven by unspecific motor-stimulant action. On the contrary, the high 30 mg/kg dose of SSR180711 significantly decreased locomotor activity; however, we did not observe any overt behavioural changes, such as other signs of sedation or poor motor coordination, at the doses tested.

Mood dysregulation is traditionally thought of as the hallmark of depression, but cognitive disturbances are also commonly found, including deficits in memory, attention and executive function (Austin et al., 2001; Castaneda et al., 2008; Herrmann et al., 2007). Cognitive deficits in depression have been reported to correlate with the severity of the depressive symptoms (Airaksinen et al., 2004). It is notable that cognitive deficits are generally not ameliorated, and sometimes even worsened, by antidepressant medication (Amado-Boccara et al., 1995; Rosenzweig-Lipson et al., 2007). Considering the immense body of preclinical and clinical evidence for pro-cognitive effects of nAChR agonists (Levin et al., 2006 and Sacco et al., 2004), incorporating nAChR stimulation into the action of future antidepressants may not only improve antidepressant efficacy, but also be a remedy for cognitive dysfunction in depression. It has indeed been hypothesised that smoking is a means of nicotine self-administration to control the emotional and cognitive disturbances that often co-occur in psychiatric disorders (Gehricke et al., 2007). In accordance with this hypothesis, it was recently shown that nicotine not only reversed stress-induced anhedonic-like responses in the rat chronic mild stress model of depression, but also reversed stress-induced cognitive impairment (Andreasen et al., 2011). Agonism of α7 nAChRs improves attention, learning and memory in both animals and humans (for review, see Thomsen et al., 2010). For instance, both PNU-282987 and SSR180711 improve performance in tests of attention and working memory (Pichat et al., 2007; Redrobe et al., 2009; Thomsen et al., 2009), and SSR180711 also increases short and long-term memory in rats (Hashimoto et al., 2008; Pichat et al., 2007; Roncarati et al., 2009).

Nicotine is a highly addictive drug, and an important concern is therefore the potential addictive liability of nAChR agonists. Nicotinic α4β2 and α7 receptors are both expressed in brain circuit involved in nicotine addiction, but α7 nAChRs appear to play a minor role in the development and maintenance of nicotine addiction, when compared to α4β2 nAChR (Changeux, 2010). For instance, α7 nAChRs do not contribute to the discriminative stimulus properties of nicotine (Stolerman et al., 2004). Also, α4β2 nAChRs, but not α7 nAChRs, activation is necessary for the establishment of nicotine self-administration model in mice (Pons et al., 2008), and a similar difference was found in the conditioned place preference model (Walters et al., 2006), two models often used to assess addictive properties of drugs. This suggests that α7 nAChR agonism *per se* may not be associated with addictive liability.

Based on the present findings, and previous reports from our laboratories, it is suggested that α7 nAChR agonism and SERT inhibition may act synergistically to produce antidepressant-like effects. The unique profile of SSR180711, comprising both α7 agonism and partial SERT inhibition, may be pivotal to the observed antidepressant-like effects in the rFST, mFST, and mTST. Considering the additional pro-cognitive effects of α7 agonists, SSR180711 may represent a concept of combining conventional monoaminergic approaches with the targeting of the α7 nAChR as a strategy to develop novel antidepressants with improved efficacy.

References

Airaksinen E, Larsson M, Lundberg I, Forsell Y. Cognitive functions in depressive disorders: evidence from a population-based study. Psychol Med 2004;34:83–91.

Amado-Boccara I, Gougoulis N, Poirier Littre MF, Galinowski A, Loo H. Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 1995;19:479–93.

Andreasen JT, Redrobe JP. Antidepressant-like effects of nicotine and mecamylamine in the mouse forced swim and tail suspension tests: role of strain, test and sex. Behav Pharmacol 2009a;20(3):286–95.

Andreasen JT, Redrobe JP. Nicotine, but not mecamylamine, enhances antidepressant-like effects of citalopram and reboxetine in the mouse forced swim and tail suspension tests. Behav Brain Res 2009b;197(1):150–6.

Andreasen JT, Olsen GM, Wiborg O, Redrobe JP. Antidepressant-like effects of nicotinic acetylcholine receptor antagonists, but not agonists, in the mouse forced swim and mouse tail suspension tests. J Psychopharmacol 2009;23(7):797–804.

Andreasen JT, Nielsen EO, Christensen JK, Olsen GM, Peters D, Mirza NR, et al. Subtype-selective nicotinic acetylcholine receptor agonists enhance the responsiveness to citalopram and reboxetine in the mouse forced swim test. J Psychopharmacol 2010;25(10):1347–56.

Andreasen JT, Henningsen K, Bate S, Christiansen S, Wiborg O. Nicotine reverses anhedonic-like response and cognitive impairment in the rat chronic mild stress model of depression: comparison with sertraline. Aug J Psychopharmacol 2011;25(8):1134–41.

Austin MP, Mitchell P, Goodwin GM. Cognitive deficits in depression: possible implications for functional neuropathology. Br J Psychiatry 2001;178:200–6.

Aznar S, Kostova V, Christiansen SH, Knudsen GM. Alpha 7 nicotinic receptor subunit is present on serotonin neurons projecting to hippocampus and septum. Synapse 2005;55(3):196–200.

Caldarone BJ, Wang D, Paterson NE, Manzano M, Fedolak A, Cavino K, et al. Dissociation between duration of action in the forced swim test in mice and nicotinic acetylcholine receptor occupancy with sazetidine, varenicline, and 5-I-A85380. Psychopharmacology (Berl) 2011;217:199–210.

Castaneda AE, Tuulio-Henriksson A, Marttunen M, Suvisaari J, Lonnqvist. A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. J Affect Disord 2008;106:1-27.

Changeux JP. Nicotine addiction and nicotinic receptors: lessons from genetically modified mice. Nat Rev Neurosci 2010;11(6):389–401.

Djuric VJ, Dunn E, Overstreet DH, Dragomir A, Steiner M. Antidepressant effect of ingested nicotine in female rats of Flinders resistant and sensitive lines. Physiol Behav 1999;67:533–7.

Ferguson SM, Brodkin JD, Lloyd GK, Menzaghi F. Antidepressant-like effects of the subtype-selective nicotinic acetylcholine receptor agonist, SIB-1508Y, in the learned helplessness rat model of depression. Psychopharmacology (Berl) 2000;152:295–303.

Galindo-Charles L, Hernandez-Lopez S, Galarraga E, Tapia D, Bargas J, Garduño J, et al. Serotoninergic dorsal raphe neurons possess functional postsynaptic nicotinic acetylcholine receptors. Synapse 2008;62(8):601–15.

Gatto GJ, Bohme GA, Caldwell WS, Letchworth SR, Traina VM, Obinu MC, et al. TC-1734: an orally active neuronal nicotinic acetylcholine receptor modulator with antidepressant, neuroprotective and long-lasting cognitive effects. CNS Drug Rev 2004;10(2):147–66.

Gehricke JG, Loughlin SE, Whalen CK, Potkin SG, Fallon JH, Jamner LD, et al. Smoking to self-medicate attentional and emotional dysfunctions. Nicotine Tob Res 2007;9 (Suppl. 4):S523–36.

Gopalakrishnan M, Buisson B, Touma E, Giordano T, Campbell JE, Hu IC, et al. Stable expression and pharmacological properties of the human alpha 7 nicotinic acetylcholine receptor. Eur J Pharmacol 1995;290:237–46.

Hashimoto K, Ishima T, Fujita Y, Matsuo M, Kobashi T, Takahagi M, et al. Phencyclidine-induced cognitive deficits in mice are improved by subsequent subchronic administration of the novel selective alpha7 nicotinic receptor agonist SSR180711. Biol Psychiatry 2008;63:92–7.

Herrmann LL, Goodwin GM, Ebmeier KP. The cognitive neuropsychology of depression in the elderly. Psychol Med 2007;37:1693–702.

Hwa Jung B, Chul Chung B, Chung SJ, Shim CK. Different pharmacokinetics of nicotine following intravenous administration of nicotine base and nicotine hydrogen tartarate in rats. J Control Release 2001;77:183–90.

Kenny PJ, File SE, Neal MJ. Evidence for a complex influence of nicotinic acetylcholine receptors on hippocampal serotonin release. J Neurochem 2000;75:2409–14.

Koyama S. Primer effects by conspecific odors in house mice: a new perspective in the study of primer effects on reproductive activities. Horm Behav 2004;46:303–10.

Levin ED, McClernon FJ, Rezvani AH. Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. Psychopharmacology (Berl) 2006;184:523–39.

Ma W, Miao Z, Novotny MV. Induction of estrus in grouped female mice (*Mus domesticus*) by synthetic analogues of preputial gland constituents. Chem Senses 1999;24:289–93.

Ma Z, Strecker RE, McKenna JT, Thakkar MM, McCarley RW, Tao R. Effects on serotonin of (−)nicotine and dimethylphenylpiperazinium in the dorsal raphe and nucleus accumbens of freely behaving rats. Neuroscience 2005;135:949–58.

Matta SG, Balfour DJ, Benowitz NL, Boyd RT, Buccafusco JJ, Caggiula AR, et al. Guidelines on nicotine dose selection for in vivo research. Psychopharmacology (Berl) 2007;190(3):269–319.

McClernon FJ, Hiott FB, Westman EC, Rose JE, Levin ED. Transdermal nicotine attenuates depression symptoms in nonsmokers: a double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2006;189:125–33.

Mihailescu S, Palomero-Rivero M, Meade-Huerta P, Maza-Flores A, Drucker-Colin R. Effects of nicotine and mecamylamine on rat dorsal raphe neurons. Eur J Pharmacol 1998;360:31–6.
Mihailescu S, Guzman-Marin R, Dominguez MC, Drucker-Colin R. Mechanisms of nicotine actions on dorsal raphe serotoninergic neurons. Eur J Pharmacol 2002;452:77–82.
Mineur YS, Picciotto MR. Nicotine receptors and depression: revisiting and revising the cholinergic hypothesis. Trends Pharmacol Sci 2010;31(12):580–6.
Munro G, Baek CA, Erichsen HK, Nielsen AN, Nielsen EO, Scheel-Kruger J, et al. The novel compound (+/−)-1-[10-((E)-3-Phenyl-allyl)-3,10-diaza-bicyclo[4.3.1]dec-3-yl]-propan −1-one (NS7051) attenuates nociceptive transmission in animal models of experimental pain; a pharmacological comparison with the combined mu-opioid receptor agonist and monoamine reuptake inhibitor tramadol. Neuropharmacology 2008;54:331–43.
Newhouse PA, Potter A, Singh A. Effects of nicotinic stimulation on cognitive performance. Curr Opin Pharmacol 2004;4:36–46.
Nowakowska E, Kus K, Florek E, Czubak A, Jodynis-Liebert J. The influence of tobacco smoke and nicotine on antidepressant and memory-improving effects of venlafaxine. Hum Exp Toxicol 2006;25:199–209.
Petersen DR, Norris KJ, Thompson JA. A comparative study of the disposition of nicotine and its metabolites in three inbred strains of mice. Drug Metab Dispos 1984;12:725–31.
Philip NS, Carpenter LL, Tyrka AR, Price LH. Nicotinic acetylcholine receptors and depression: a review of the preclinical and clinical literature. Psychopharmacology (Berl) 2010;212(1):1-12.
Pichat P, Bergis OE, Terranova JP, Urani A, Duarte C, Santucci V, et al. SSR180711, a novel selective alpha7 nicotinic receptor partial agonist: (II) efficacy in experimental models predictive of activity against cognitive symptoms of schizophrenia. Neuropsychopharmacology 2007;32(1):17–34.
Pons S, Fattore L, Cossu G, Tolu S, Porcu E, McIntosh JM, et al. Crucial role of α4 and α6 nicotinic acetylcholine receptor subunits from ventral tegmental area in systemic nicotine self-administration. J Neurosci 2008;28:12318–27.
Redrobe JP, Nielsen EØ, Christensen JK, Peters D, Timmermann DB, Olsen GM. Alpha7 nicotinic acetylcholine receptor activation ameliorates scopolamine-induced behavioural changes in a modified continuous Y-maze task in mice. Eur J Pharmacol 2009;602(1):58–65.
Reuben M, Clarke PB. Nicotine-evoked [3H]5-hydroxytryptamine release from rat striatal synaptosomes. Neuropharmacology 2000;39:290–9.
Ribeiro EB, Bettiker RL, Bogdanov M, Wurtman RJ. Effects of systemic nicotine on serotonin release in rat brain. Brain Res 1993;621:311–8.
Roncarati R, Scali C, Comery TA, Grauer SM, Aschmi S, Bothmann H, et al. Procognitive and neuroprotective activity of a novel alpha7 nicotinic acetylcholine receptor agonist for treatment of neurodegenerative and cognitive disorders. J Pharmacol Exp Ther 2009;329:459–68.
Rosenzweig-Lipson S, Beyer CE, Hughes ZA, Khawaja X, Rajarao SJ, Malberg JE, et al. Differentiating antidepressants of the future: efficacy and safety. Pharmacol Ther 2007;113:134–53.
Sacco KA, Bannon KL, George TP. Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders. J Psychopharmacol 2004;18:457–74.
Stolerman IP, Chamberlain S, Bizarro L, Fernandes C, Schalkwyk L. The role of nicotinic receptor α 7 subunits in nicotine discrimination. Neuropharmacology 2004;46:363–71.
Thomsen MS, Christensen DZ, Hansen HH, Redrobe JP, Mikkelsen JD. alpha(7) Nicotinic acetylcholine receptor activation prevents behavioral and molecular changes induced by repeated phencyclidine treatment. Neuropharmacology 2009;56(6–7):1001–9.
Thomsen MS, Hansen HH, Timmerman DB, Mikkelsen JD. Cognitive improvement by activation of alpha7 nicotinic acetylcholine receptors: from animal models to human pathophysiology. Curr Pharm Des 2010;16(3):323–43.
Tizabi Y, Overstreet DH, Rezvani AH, Louis VA, Clark Jr E, Janowsky DS, et al. Antidepressant effects of nicotine in an animal model of depression. Psychopharmacology (Berl) 1999;142:193–9.
Tizabi Y, Getachew B, Rezvani AH, Hauser SR, Overstreet DH. Antidepressant-like effects of nicotine and reduced nicotinic receptor binding in the fawn-hooded rat, an animal model of co-morbid depression and alcoholism. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:398–402.
Tucci SA, Genn RF, File SE. Methyllycaconitine (MLA) blocks the nicotine evoked anxiogenic effect and 5-HT release in the dorsal hippocampus: possible role of alpha7 receptors. Neuropharmacology 2003;44(3):367–73.
University of California Breeding Information. http://research.uci.edu/tmf/husbandry.htm 2011.
Vazquez-Palacios G, Bonilla-Jaime H, Velazquez-Moctezuma J. Antidepressant effects of nicotine and fluoxetine in an animal model of depression induced by neonatal treatment with clomipramine. Prog Neuropsychopharmacol Biol Psychiatry 2005;29:39–46.
Walters CL, Brown S, Changeux JP, Martin B, Damaj MI. The β2 but not α7 subunit of the nicotinic acetylcholine receptor is required for nicotine conditioned place preference in mice. Psychopharmacology (Berl) 2006;184:339–44.
Willner P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. Neuropsychobiology 2005;52(2):90-110.