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European Journal of Pharmacology 426 (2001) R1–R2

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Rapid communication

The selective σ_1 receptor agonist, 1-(3,4-dimethoxyphenethyl)-4-(phenylpropyl) piperazine (SA4503), blocks the acquisition of the conditioned place preference response to (−)-nicotine in rats

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Received 17 July 2001; accepted 20 July 2001

Abstract

We examined the effect of the σ_1 receptor agonist, 1-(3,4-dimethoxyphenethyl)-4-(phenylpropyl)piperazine (SA4503), on the acquisition of the conditioned place preference response to subcutaneously administered (−)-nicotine in rats. (−)-Nicotine, but not SA4503 or vehicle, produced a significant conditioned place preference response. Pretreatment of animals with either 1 or 3 mg/kg of SA4503 significantly attenuated the conditioned place preference response to (−)-nicotine. © 2001 Published by Elsevier Science B.V.

Keywords: Conditioned place preference; Nicotine; σ Receptor

(−)-Nicotine, one of the major chemical components of cigarettes, interacts with nicotinic acetylcholine receptors in the brain to produce its rewarding effects. Thus, strategies for treating smoking include developing compounds that antagonize its action at nicotinic acetylcholine receptors (i.e., antagonists or partial agonists) or alter acetylcholine levels. Interestingly, nicotine-induced changes in catecholamine release are decreased by compounds that interact with σ_1 receptors (Paul et al., 1993). Furthermore, σ_1 receptors are neuromodulators of nicotinic acetylcholine receptors (Maurice et al., 1999).

The compound SA4503, a selective σ_1 receptor agonist, increases acetylcholine levels, produces nootropic actions and antagonizes the action of cholinergic antagonists (Kobayashi et al., 1996; Matsuno et al., 1996; Senda et al., 1997). Therefore, in this study, we examined the effect of SA4503 on nicotine's action in the conditioned place preference paradigm in rats. The conditioned place preference paradigm is believed to be a measure of the incentive motivational value of a stimulus.

Male Sprague-Dawley rats (175–200 g; Taconic Farms, Germantown, NY) were habituated and handled as previously described (Dewey et al., 1998). A three-chambered conditioned place preference apparatus, as described previously (Dewey et al., 1998), was used. Animals were randomly assigned to receive either vehicle (1 ml/kg subcutaneously of 0.9% saline) or i.p. SA4503 30 min prior to receiving either vehicle or nicotine (0.6 mg/kg subcutaneously). Following the administration of either vehicle or nicotine, animals were confined to one of two conditioning chambers for 30 min during each pairing session using a counterbalanced design. The treatment groups were: vehicle/vehicle, vehicle/nicotine, vehicle/3 mg/kg SA4503, 1 mg/kg SA4503/nicotine and 3 mg/kg SA4503/nicotine. All animals received eight pairings each (one injection per day). On the test day, the animals were allowed access to the entire apparatus for 15 min. The amount of time spent in each chamber was recorded using

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0014-2999/01/$ - see front matter © 2001 Published by Elsevier Science B.V.
PII: S0014-2999(01)01229-8

Table 1
Effect of the intraperitoneal administration of vehicle and SA4503 on the acquisition of the conditioned place preference response to 0.6 mg/kg s.c. of (−)-nicotine in male Sprague-Dawley rats

Treatment pairing, paired/unpaired	Drug given before pairing	Time spent in chamber (min)	
		Paired	Unpaired
Vehicle/vehicle	Vehicle[a]	7.2 ± 0.3[b]	7.8 ± 0.3
Nicotine/vehicle	Vehicle	9.6 ± 0.5[c]	5.4 ± 0.5
Vehicle/vehicle	SA4503, 3 mg/kg	7.6 ± 0.3	7.4 ± 0.3
Nicotine/vehicle	SA4503, 1 mg/kg	8.1 ± 0.3	5.9 ± 0.3
Nicotine/vehicle	SA4503, 3 mg/kg	7.7 ± 0.2	6.3 ± 0.2

[a] The vehicle was 1 ml/kg s.c. of 0.9% saline.

[b] Each value represents the mean number of minutes spent in each chamber ± S.E.M. Ten rats were examined for each treatment pairing. For treatment pairings, all animals were subjected to eight pairings and received the appropriate treatment (drug given before pairing) 30 min before confinement in the appropriate chamber. On the test day, the animals were allowed access to the all chambers for 15 min and the time spent in each chamber was automatically recorded.

[c] Significantly greater than all other groups, $P < 0.01$, ANOVA and Dunnett's test.

an automated recording device. The data were expressed as the raw time spent in each chamber. The data were analyzed using a one-way analysis of variance followed by Dunnett's post hoc test.

The results are presented in Table 1. As previously reported (Dewey et al., 1998), the subcutaneous administration of nicotine produced a significant conditioned place preference response (analysis of variance, $F(4,45) = 7.73$, $P < 0.0001$). In contrast, the pairing of animals with either vehicle/vehicle or vehicle/3 mg/kg SA4503 did not elicit a significant conditioned place preference or aversion (Table 1). However, the administration of either 1 or 3 mg/kg i.p. of SA4503 prior to pairing with nicotine significantly attenuated the conditioned place preference response to nicotine (Table 1).

Our results indicate that SA4503 significantly attenuates the acquisition of the conditioned place preference response to nicotine. It seems unlikely that SA4503 interfered with the acquisition of the nicotine conditioned place preference response by producing an aversive or appetitive effect, since SA4503 alone did not produce conditioned place preference or aversion. It also seems unlikely that SA4503 is altering the ability of the animals to associate the effects of nicotine with the appropriate chamber as SA4503 has been shown to possess nootropic, not amnestic, properties (Senda et al., 1997).

The mechanism by which SA4503 alters the acquisition of the conditioned place preference response to nicotine is unknown. It is believed that nicotine may produce its rewarding/reinforcing effects by activating nicotinic acetylcholine receptors on neurons in various brain areas, particularly mesolimbic areas (Nisell et al., 1995). Therefore, it is possible that SA4503 may diminish nicotine's behavioral effects by acting as a nicotinic acetylcholine receptor antagonist. However, SA4503 does not have appreciable affinity for nicotinic acetylcholine receptors (Matsuno et al., 1996). The systemic administration of SA4503 produces a significant increase in extracellular acetylcholine levels in the hippocampus and frontal cortex of freely moving rats (Kobayashi et al., 1996). This could potentially diminish nicotine's action via competition of acetylcholine for nicotinic cholinergic receptors, although this remains to be proven.

In conclusion, SA4503 significantly attenuates the acquisition of the conditioned place preference response to subcutaneously administered nicotine. It has been hypothesized that the conditioned place preference paradigm measures the appetitive or incentive motivational value of a particular stimulus (Gardner, 1997). Therefore, SA4503 may diminish the appetitive value of nicotine.

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