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Both $GABA_B$ receptor activation and blockade exacerbated anhedonic aspects of nicotine withdrawal in rats

Styliani Vlachou [a], Neil E. Paterson [a,1], Sebastien Guery [b,2], Klemens Kaupmann [b], Wolfgang Froestl [b,3], Deboshri Banerjee [c,4], M.G. Finn [c], Athina Markou [a,*]

[a] Department of Psychiatry, School of Medicine, University of California San Diego, La Jolla, CA 92093-0603, USA
[b] Neuroscience Research, Novartis Institutes for Biomedical Research, Novartis Pharma AG, Basel, Switzerland
[c] Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037, USA

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ABSTRACT

Nicotine dependence is maintained by the aversive, depression-like effects of nicotine withdrawal and the rewarding effects of acute nicotine. $GABA_B$ receptor antagonists exhibit antidepressant-like effects in rodents, whereas $GABA_B$ receptor agonists attenuate the rewarding effects of nicotine. Recent studies with $GABA_B$ receptor positive modulators showed that these compounds represent potentially improved medications for the treatment of nicotine dependence because of fewer side-effects than $GABA_B$ receptor agonists. Thus, $GABA_B$ receptor agonists and antagonists, and $GABA_B$ receptor positive modulators may have efficacy as smoking cessation aids by targeting different aspects of nicotine dependence and withdrawal. The present study assessed the effects of the $GABA_B$ receptor agonist CGP44532, the $GABA_B$ receptor antagonist CGP56433A, and the $GABA_B$ receptor positive modulator BHF177 on the anhedonic aspects of nicotine withdrawal. Rats were prepared with stimulating electrodes in the posterior lateral hypothalamus. After establishing stable intracranial self-stimulation (ICSS) thresholds, rats were prepared with subcutaneous osmotic minipumps delivering either nicotine or saline for 7 or 14 days. ICSS thresholds were assessed 6 h post-pump removal. Thirty hours after pump removal, CGP44532, CGP56433A, and BHF177 were administered 30 min prior to ICSS testing. Both $GABA_B$ receptor activation (CGP44532 and BHF177) and blockade (CGP56433A) elevated ICSS thresholds in all groups, resulting in exacerbated effects of nicotine withdrawal in the nicotine-treated groups. These similar effects of $GABA_B$ receptor activation and blockade on the anhedonic depression-like aspects of nicotine withdrawal were surprising and perhaps reflect differential efficacy of these compounds at presynaptic hetero- and autoreceptors, as well as postsynaptic, $GABA_B$ receptors.

1. Introduction

γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain, acting through ionotropic $GABA_A$ and $GABA_C$ and metabotropic $GABA_B$ receptors. $GABA_B$ receptors are crucial in neurotransmission (Bowery et al., 2002), the pathophysiology of depression (Cryan and Slattery, 2010), and the modulation of reward processes (for review, Vlachou and Markou, 2010). Thus, $GABA_B$ receptors are a promising target for the treatment of drug, including nicotine, dependence that is characterized by alterations in reward processes [(for reviews, Buchhalter et al., 2008; Cryan et al., 2003b; Vlachou and Markou, 2010)].

Findings supporting a role of GABA transmission in nicotine dependence include observations that acute nicotine administration modulates inhibitory GABAergic and excitatory glutamatergic inputs to ventral tegmental area (VTA) dopaminergic neurons (Mansvelder et al., 2002). The VTA to nucleus accumbens dopaminergic projection is a critical component of the neurocircuit involved in drug dependence (Di Chiara and Imperato, 1988). Thus, chronic nicotine exposure could induce neuroadaptations in $GABA_B$ receptor number/function, in addition to changes in other neurotransmitter systems/receptors, that could contribute to the depression-like aspects of nicotine withdrawal. The depression-like aspects of nicotine withdrawal are an important motivational factor in the perpetuation of the harmful tobacco smoking habit in humans (Hughes, 2007; Kenny and Markou, 2001).

* Corresponding author at: Department of Psychiatry M/C 0603, School of Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA. Tel.: +1 858 534 1572; fax: +1 858 534 9917.
E-mail address: amarkou@ucsd.edu (A. Markou).
[1] Present address: PsychoGenics, Inc., 765 Old Saw Mill River Road, Tarrytown, NY 10591, USA.
[2] Present address: Place Marie Jose 6, 1050 Bruxelles, Belgium.
[3] Present address: AC Immune SA, EPFL, PSE Building B 1.7, CH-1015 Lausanne, Switzerland.
[4] Present address: Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.

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Emerging, but contradictory, evidence from clinical and preclinical studies implicates changes in GABAergic function in the pathophysiology of non-drug-induced depression. Specifically, acute administration of $GABA_B$ receptor antagonists exerted antidepressant-like effects in the forced swim test in rats (Frankowska et al., 2007; Slattery et al., 2005), mice and olfactory bulbectomized rats (Nowak et al., 2006). Furthermore, repeated administration of a $GABA_B$ receptor antagonist attenuated decreases in sucrose consumption, a measure of hedonia, seen after exposure to chronic mild stress (Nowak et al., 2006) and improved learned helplessness in rats (Nakagawa et al., 1999; but see Sufka et al., 2009). Consistent with these findings, $GABA_{B1}$ knockout mice displayed antidepressant-like behavior (Jacobson et al., 2007a; Jacobson and Cryan, 2005; Mombereau et al., 2004, 2005). Thus, blockade or loss of $GABA_B$ receptor function induces an antidepressant-like phenotype in rodents.

In contrast to rodent studies, clinical studies showed decreased GABA levels in plasma, cerebrospinal fluid, and cortex in depressed individuals (Sanacora et al., 2004, 2006; for review, Sanacora and Saricicek, 2007), suggesting that $GABA_B$ receptor agonists or positive modulators, rather than antagonists, may have antidepressant properties (Esel et al., 2008; Pilc and Nowak, 2005; but see (Nakagawa et al., 1996a,b,c; Slattery et al., 2005). In contradiction to the aforementioned clinical studies, $GABA_B$ receptor agonists and positive modulators exhibited antidepressant-like effects in the forced swim test in rats (Frankowska et al., 2007).

In rodents, the depression-like aspects of nicotine withdrawal are reflected in elevated intracranial self-stimulation (ICSS) reward thresholds (Epping-Jordan et al., 1998). The present study aimed to evaluate whether agonism or antagonism at $GABA_B$ receptors would ameliorate the depression-like aspects of nicotine withdrawal by assessing the effects of a $GABA_B$ receptor agonist, antagonist, and positive allosteric modulator on nicotine withdrawal-induced elevations in ICSS reward thresholds.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Charles River, Raleigh, NC) weighing 300–350 g upon arrival in the laboratory were group housed on a 12 h/12 h reverse light/dark cycle with unrestricted access to water except during testing. Behavioral testing occurred during the dark phase of the light/dark cycle. All subjects, animal facilities, and experimental protocols were in accordance with National Institutes of Health (National Research Counsil, 1996) and Association for the Assessment and Accreditation of Laboratory Animal Care guidelines and were approved by the Institutional Animal Research Committee.

2.2. Drugs

(−)Nicotine hydrogen tartrate (Sigma, St. Louis, MO) was dissolved in saline (pH adjusted to 7.0 ± 0.5 with sodium hydroxide). The solution was then filtered through a 0.22 μm syringe filter (Fisher Scientific, Pittsburgh, PA) for sterilization. Nicotine doses are reported as free base concentrations, while all doses of $GABA_B$ receptor ligands are reported as salt concentrations. 3-amino-2[*S*]-hydroxypropyl-methylphosphinic acid (CGP44532; compound #63 in Froestl et al., 1995), [3-{1-(*S*)-[{3-(cyclohexylmethyl)hydroxylphosphinyl}-2-(*S*) hydroxypropyl]amino}ethyl]benzoic acid (CGP56433A; Table IV in Froestl et al., 1996), and *N*-[(1*R*,2*R*,4*S*)-bicyclo[2.2.1]hept-2-yl]-2-methyl-5-[4-(trifluoromethyl)phenyl]-4-pyrimidinamine (BHF177; compound #27 in Guery et al., 2007) were synthesized and provided by SG and WF or DB and MGF, respectively. In GTPγ^{35}S assays on CHO-K1 membranes from GABA-$B_{(1b/2)}$ co-expressing cells, the potency of BHF177 was 1.7 μM (measured at 1 μM GABA; Guery et al., 2007), similar to that of other positive modulators (CGP7930 and GS39783; Urwyler et al., 2001, 2003), although BHF177 is structurally different from CGP7930 and GS39783. CGP44532 and CGP56433A were dissolved in 0.9% saline and administered subcutaneously (1 ml/kg, 30 min pretreatment time). BHF177 was suspended in 0.5% methylcellulose and administered intraperitoneally (2 ml/kg, 30 min pretreatment time). The different routes of administration used in these experiments were selected for direct comparisons with previous studies assessing the effects of $GABA_B$ receptor agonists and antagonists on performance in the ICSS task (Macey et al., 2001; Paterson et al., 2008b).

2.3. Apparatus

Sixteen Plexiglas chambers were used (30.5 × 30 × 17 cm; Med Associates, St. Albans, VT), each housed in a sound-attenuating box (San Diego Instruments, San Diego, CA). Each chamber contained a metal wheel manipulandum (5 cm wide), centered in a side wall, that required ~0.2 N force for a quarter turn rotation. Brain stimulation was delivered by constant current stimulators (Stimtech 1200, San Diego Instruments, San Diego, CA). Subjects were connected to the stimulation circuit with bipolar leads (Plastics One, Roanoke, VA) attached to gold-contact swivel commutators (model SL2C, Plastics One, Roanoke, VA).

2.4. ICSS electrode placement

Rats were anesthetized with an isoflurane/oxygen vapor mixture (1–1.5%) and placed in a stereotaxic frame (David Kopf Instruments, Tujunga, CA). Stainless steel bipolar electrodes (11 mm, model MS303/2, Plastics One, Roanoke, VA) were implanted in the posterior lateral hypothalamus (anterior/posterior, −0.5 mm from bregma; medial/lateral, ±1.7 mm; dorsal/ventral, −8.3 mm from dura; with the incisor bar 5 mm above the interaural line; Paxinos and Watson, 1998).

2.5. Osmotic minipump implantation

Rats were anesthetized with an isoflurane/oxygen vapor mixture (1–1.5%), and an osmotic minipump (models 2ML1 and 2ML2, Alza Corp., Palo Alto, CA, USA) was inserted subcutaneously, as described previously (Der-Avakian and Markou, 2010; Paterson et al., 2007). Minipumps were removed on day 7 (Experiments 1 and 2) or day 14 (Experiment 3) under anesthesia.

2.6. Behavioral procedures

2.6.1. ICSS training

The discrete-trial current-threshold procedure was a modification of a task initially developed by Kornetsky and Esposito (1979) and described in detail elsewhere (Markou and Koob, 1992). The rats were first trained to turn the wheel manipulandum on a fixed-ratio 1 (FR1) schedule of reinforcement. Each quarter turn of the wheel resulted in the delivery of a 500 ms train of 0.1 ms cathodal square-wave pulses at a frequency of 100 Hz. After successful acquisition of responding for stimulation on this FR1 schedule (100 reinforcements within 10 min), the rats were trained gradually on the discrete-trial current-threshold procedure.

Each trial began with the delivery of a noncontingent electrical stimulus, followed by a 7.5 s response window within which the subject could make a response to receive a second contingent stimulus identical to the initial noncontingent stimulus. A response during this time window was labeled a positive response, whereas the lack of a response was labeled a negative response. During a 2 s period immediately after a positive response, additional responses had no consequence. The intertrial interval that followed either a positive response or the end of the response window in the case of a negative