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Selective activation of the trace amine-associated receptor 1 decreases cocaine's reinforcing efficacy and prevents cocaine-induced changes in brain reward thresholds

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ABSTRACT

The newly discovered trace amine-associated receptor 1 (TAAR1) has emerged as a promising target for medication development in stimulant addiction due to its ability to regulate dopamine (DA) function and modulate stimulants' effects. Recent findings indicate that TAAR1 activation blocks some of the abuse-related physiological and behavioral effects of cocaine. However, findings from existing self-administration studies are inconclusive due to the very limited range of cocaine unit doses tested. Here, in order to shed light on the influence of TAAR1 on cocaine's reward and reinforcement, we studied the effects of partial and full activation of TAAR1on (1) the dose–response curve for cocaine self-administration and (2) cocaine-induced changes in intracranial self-stimulation (ICSS). In the first experiment, we examined the effects of the selective full and partial TAAR1 agonists, RO5256390 and RO5203648, on self-administration of five unit-injection doses of cocaine (0.03, 0.1, 0.2, 0.45, and 1 mg/kg/infusion). Both agonists induced dose-dependent downward shifts in the cocaine dose–response curve, indicating that both partial and full TAAR1 activation decrease cocaine, reinforcing efficacy. In the second experiment, RO5256390 and the partial agonist, RO5263397, dose-dependently prevented cocaine-induced lowering of ICSS thresholds. Taken together, these data demonstrated that TAAR1 stimulation effectively suppresses the rewarding and reinforcing effects of cocaine in self-administration and ICSS models, supporting the candidacy of TAAR1 as a drug discovery target for cocaine addiction.

1. Introduction

Cocaine addiction is a chronic relapsing disease for which effective pharmacotherapies are lacking (Karila et al., 2011). Changes in dopamine (DA) transmission occurring during and after cocaine exposure are believed to contribute critically to drug reinforcement (Volkow et al., 1997), withdrawal (Rossetti et al., 1992; Weiss et al., 1992), and relapse (Volkow et al., 2006). Consequently, the search for effective pharmacotherapies has primarily focused on developing pharmacological agents able to alter the DA system, by either acting as a substitute for the stimulant drug or exerting antagonistic actions through preventing binding of the stimulant to the dopamine transporter (DAT) (Gorelick et al., 2004; Rothman et al., 2008). However, one of the shortcomings of DA-based therapies is the emergence of side effects, particularly after prolonged exposure. In this context, the recently discovered trace amine-associated receptor 1 (TAAR1), by virtue of its unique ability to modulate DA function, has arisen as a novel therapeutic target to treat cocaine addiction (Revel et al., 2012; Sotnikova et al., 2009).

TAAR1 belongs to a family of G protein-coupled receptors that was found to be activated by trace amines (TAs) (Borowsky et al., 2001; Bunzow et al., 2001), a group of endogenous amines that have long been implicated in the psychoactive actions of motor stimulants (Berry, 2004; Burchett and Hicks, 2006). TAAR1 is expressed in brain monoaminergic nuclei and colocalized with the DAT in a subset of DA neurons (Borowsky et al., 2001; Lindemann et al., 2008; Xie and Miller, 2007). Genetic deletion of *Taar1* leads to elevated spontaneous discharge of DA neurons in the ventral tegmental area (VTA) (Lindemann et al., 2008), increased DA level in the nucleus accumbens (NAc) (Leo et al., 2014), enhanced sensitivity to psychostimulant-induced hyperactivity, and conditioned place preference (CPP) (Achat-Mendes et al., 2012) and elevated striatal DA release (Lindemann et al., 2008; Wolinsky et al., 2007). Taken together, these observations indicate that TAAR1 is a key neuromodulator of DA transmission.

Abbreviations: ANOVA, analysis of variance; CPP, conditioned place preference; DA, dopamine; DAT, dopamine transporter; FR1, fixed ratio 1; ICSS, intracranial self-stimulation; i.p., intraperitoneal; i.v., intravenous; NAc, nucleus accumbens; N-K, Newman-Keuls; PE-50, polyethylene-50; TAAR1, trace amine-associated receptor 1; TAs, trace amines; VTA, ventral tegmental area.

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Several highly selective TAAR1 ligands have become recently available, opening the door for direct investigation of the specific physiological and behavioral effects of pharmacological activation of this receptor. DA neuron firing frequency in the VTA was shown to be decreased by a full TAAR1 agonist (Revel et al., 2011, 2013) and increased by an antagonist and a partial agonist (Revel et al., 2012, 2013; Bradaia et al., 2009). In animal models, several TAAR1 agonists demonstrated an ability to suppress cocaine-induced locomotor hyperactivity (Revel et al., 2011, 2012), behavioral sensitization (Thorn et al., 2014b), CPP (Thorn et al., 2014a), and reinstatement of cocaine seeking (Pei et al., 2014; Thorn et al., 2014a), as well as cocaine-stimulated DA overflow in the NAc (Pei et al., 2014). However, there has been no systematic examination of the functional contribution of TAAR1 to the rewarding and reinforcing effects of cocaine. Although existing evidence indicates that TAAR1 activation suppresses cocaine self-administration, only a limited range of cocaine unit doses have been examined (Pei et al., 2014; Revel et al., 2012; Thorn et al., 2014a), making it difficult to determine whether reduced cocaine taking is due to agonistic or antagonistic actions of TAAR1 on cocaine reinforcement.

To address this important question, one objective of the present study was to examine the shifts produced by selective partial and full TAAR1 agonism on the dose–response curve for cocaine self-administration. A second objective was to study the impact of TAAR1 activation on cocaine's ability to alter brain reward. The facilitating effects of cocaine on brain reward function can be modeled in the intracranial self-stimulation (ICSS) paradigm and are manifested as a decrease in ICSS thresholds (Wise, 1996). Consequently, we used this well-validated model to assess the effects of partial and full TAAR1 agonists on cocaine-induced reductions in ICSS thresholds.

2. Experimental procedures

2.1. Subjects

Male Long–Evans rats (n = 36) were sourced from the University of Canterbury and male Wistar rats (n = 24) from F. Hoffmann-La Roche Ltd (Basel, Switzerland). All animals were housed in temperature- and humidity-controlled colony rooms with a 12-hr light/dark cycle (lights off at 8 AM). Rats for the ICSS experiments were given food ad libitum. Rats in the cocaine dose–response experiments were given a maintenance diet and kept at 100% of the weight; they were at 7 days post-surgery (Ferragud et al., 2009). Water was given at ad libitum at all times. Animal care and experimental protocols were approved by the Animal Ethics Committee of the University of Canterbury or the City of Basel Cantonal Animal Protection Committee. All experiments were approved by the ethics committee affiliated to each institution. The dose–response experiments were conducted at the University of Canterbury and the ICSS experiments were performed at F. Hoffmann-La Roche Ltd.

2.2. Pharmacological agents

Cocaine hydrochloride was obtained from the National Institute on Drug Abuse (USA) and dissolved in 0.9% physiological saline for intraperitoneal (i.p.) injection and intravenous (i.v.) self-administration. RO5203648, RO5263397 (partial TAAR1 agonists) and RO5256390 (full TAAR1 agonist) were synthesized at F. Hoffman-La Roche Ltd. In the cocaine dose–response experiment, the TAAR1 agonists were dissolved in 10% dimethylsulfoxide and 0.9% physiological saline. In the ICSS assay, RO5263397 and RO5256390 were dissolved in 0.3% Tween 80 and 0.9% physiological saline. The main difference between these drugs is the partial agonism of RO5203648 (59%) and RO5263397 (76%) on rat TAAR1 versus the full agonist efficacy of RO5256390 (107%) (Revel et al., 2012, 2013). Although the two partial agonists are from a different chemical subseries than the full agonist, their pharmacokinetic profile is very similar in rats, while the same dose of the full agonist RO5256390 yields less brain exposure. Overall, the two partial agonists behaved very similar in behavioral and electrophysiological tests (Revel et al., 2012, 2013).

2.3. Cocaine self-administration training and tests

Rats (n = 36) were anesthetized with ketamine (85 mg/kg, i.p.) and domitor (medetomidine, 0.35 mg/kg, i.p.). The analgesic carprofen was administered before surgery (5 mg/kg, i.p.). Surgery was performed as described previously (Velazquez-Sanchez et al., 2011, 2013). Briefly, catheters (O/D 0.63 mm, I/D 0.30 mm, Camcaths, Cambridge, UK) were implanted into the right jugular vein, exiting dorsally between the scapulae. Analgesic and antiseptic cream was applied to the back and neck incision areas after suturing. On completion of surgery, rats were given Antisedan (atipamezole, 1.0 mg/kg, i.p.) to reverse the anesthesia. To prevent infection, rats were treated with antibiotic (Cephalexin, 50 mg/kg, s.c.) during the 1 day prior to surgery and on the day of surgery. Catheters were flushed with heparinized saline (0.1 ml, 70 IU/ml) before and after each self-administration session.

Twelve self-administration chambers (Med Associates, VT, USA) controlled by software (Med-PC IV®) were used in the cocaine dose–response studies. Chambers had two response levers designated as active and inactive. Active lever presses resulted in activation of the infusion pump and delivery of cocaine, and illumination of a light stimulus for 5 sec. Presses on the inactive lever were recorded but had no programmed consequences. Each experimental chamber was enclosed in a sound-attenuating box. The house light was on throughout training and test sessions. Rats were connected to a liquid swivel with polyethylene-50 (PE-50) tubing protected by a metal spring.

All the rats were firstly trained to lever press to self-administer cocaine (0.45 mg/kg per infusion in 100 μl, over 5 s) under a fixed-ratio 1 (FR1) schedule of reinforcement in daily 60 min sessions. After the responses met the stability criterion (number infusions per session ≥ 12 for 3 consecutive days with less than 20% variance in the last 3 days), rats were randomly assigned to five groups that self-administered cocaine either at the same dose (0.45 mg/kg/infusion) or at a substitute dose (1.0, 0.2, 0.1, or 0.03 mg/kg/infusion). The new dose of cocaine was maintained until a criterion of stability was met (less than 10% variation in the last 3 days). The amount of cocaine was limited throughout to a maximum of 20 mg/kg per session to prevent overdose.

Two experiments were performed, one for each of the two TAAR1 agonists. After training, each rat was subjected to five cocaine intake tests in which a pre-treatment of RO5203648 (3 or 6 mg/kg, i.p.), RO5256390 (3 or 6 mg/kg, i.p.), or vehicle was administered 15 min before the cocaine self-administration session (60 min). The five cocaine intake tests were administered in randomized order. The test days were separated by at least 2 days during which rats undertook regular cocaine self-administration sessions until their response returned to their original response level. The same values for the control condition (i.e., vehicle followed by cocaine S-A) were used in the two experiments.

2.4. ICSS experiments

Rats (n = 24) were anesthetized with sodium ketamine hydrochloride 5% (90 mg/kg i.p.) and xylazine 2% (10 mg/kg i.p.) and administered buprenorphine (Temgesic, 0.025 mg/kg s.c.). Properly-insulated stainless-steel bipolar electrodes (MS 303/3, Plastics One Inc., Roanoke, VA, USA) were stereotaxically implanted unilaterally in the mesolimbic system at the level of the VTA (6.7 mm posterior to bregma, 0.3 mm lateral from the midline suture, and 8.5 mm ventral from the skull surface). Electrode tips were approximately 0.5 mm apart in the dorsoventral plane. Electrodes were implanted perpendicular to the horizontal plane, and the incisor bar adjusted to place lambda and bregma in the same horizontal plane. The electrode assembly was secured to the skull by 4–5 stainless-steel screws and an autopolymerizing resin. Animals were maintained post-operatively in a warm environment until