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Research report

Involvement of the rostral agranular insular cortex in nicotine self-administration in rats

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HIGHLIGHTS

- We inactivated the rostral agranular insular cortex (RAIC) using baclofen/muscimol.
- RAIC inactivation reduced nicotine self-administration under fixed ratio-5 schedule.
- RAIC inactivation also attenuated cue-induced reinstatement of nicotine seeking.
- Food self-administration (fixed ratio-5 schedule) unaffected by RAIC inactivation.

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ABSTRACT

Our prior work demonstrated the involvement of the caudal granular subregion of the insular cortex in a rat model of nicotine self-administration. Recent studies in various animal models of addiction for nicotine and other drugs have identified a role for the rostral agranular subregion (RAIC). The current research was undertaken to examine the involvement of the RAIC in a rat model of nicotine self-administration. We investigated the inactivating effects of local infusions of a γ-aminobutyric acid agonist mixture (baclofen/muscimol) into the RAIC on nicotine self-administration under a fixed-ratio 5 (FR-5) schedule and on reinstatement of nicotine seeking induced by nicotine-associated cues in rats. We also evaluated the effects of RAIC inactivation on food self-administration under an FR5 schedule as a control. Inactivation of the RAIC decreased nicotine, but not food, self-administration. RAIC inactivation also prevented the reinstatement, after extinction, of nicotine seeking induced by nicotine-associated cues. Our study indicates that the RAIC is involved in nicotine-taking and nicotine-seeking in rats. Modulating insular cortex function appears to be a promising approach for nicotine dependence treatment.

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1. Introduction

Over 5 million deaths per year worldwide result from tobacco-related diseases and this number is expected to double within the next decade [1], making tobacco smoking a major population health issue. Though multiple medications have been approved for the indication of smoking cessation, the relapse rate of smokers attempting to quit remains quite high [2,3]. Considering that nicotine is the primary psychoactive component of tobacco, there is a need to understand the neurocircuitry underlying its role in both smoking behavior and relapse.

Recent focus in this regard has examined the insular cortex, or insula, a brain area involved in interoception and thus in numerous behaviors including conscious urges, anxiety, pain, cognition, mood and substance abuse [4–10]. The insula has become more accepted as a critical substrate underlying addiction [11], particularly since the 2007 findings of Naqvi and colleagues which observed stroke-induced damage to the insular cortex being

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correlated to immediate smoking cessation easily achieved without craving or relapse. Though many human imaging studies followed [12], animal models have been critical to examine the effects of manipulating insular cortex function in various aspects of nicotine addiction [13–17].

The granular, dysgranular, and agranular corticies are the three structurally and functionally distinct subregions that comprise the insula [18]. Our previous studies [14,17], along with the work of others [15], have demonstrated that the caudal granular insular cortex (CGIC) plays an important role in rodent models of nicotine addiction. The CGIC integrates nociceptive [19] and unimodal viscerosensory [20] afferents from the thalamus along with those from the somatosensory cortex. It also primarily sends efferent projections back to those areas as well as to the caudate-putamen [21]. Through the dysgranular insular subregion, information initially integrated in the CGIC is relayed and further integrated before reaching the rostral agranular insular cortex (RAIC) [22]. Importantly, the granular insular cortex is the only insular subregion lacking projections to nuclei within the amygdala [22].

The RAIC send efferents to the ventral striatum [23,24] and the lateral nucleus accumbens [22,25,26], while having reciprocal connections with the basolateral amygdala and the prelimbic cortex [22,27]. As it receives afferents from the high-order [28] medial subdivision of the mediodorsal thalamic nucleus [29,30], along with those from multiple medial thalamic nuclei conveying motivational/affective aspects of peripheral stimuli, the RAIC is considered a high-order multimodal cortical region. The involvement of the RAIC has also been observed in certain models of nicotine addiction [16,31] and neural responses to nicotine exposure [32,33] in rodents.

The current study examined whether the RAIC was involved in nicotine self-administration and seeking behavior, as we have previously observed with the CGIC. Thus, the same intracranial manipulations were used in the current study as used previously with the CGIC: bilateral infusions of γ-aminobutyric acid (GABA) receptor agonists, baclofen and muscimol, into the RAIC. Food self-administration was also evaluated as a control.

2. Materials and methods

2.1. Subjects

Naive male Long-Evans rats (Charles River, Lachine, QC) weighing 300–325 g at the start of experiments were maintained on ~20 g of rat chow daily and ad libitum water while in their home cages. Animals were single-housed in a temperature-controlled room on a 12 h reverse light cycle with all behavioral testing occurring during the dark phase. All experimental procedures described in this report were carried out in compliance with the guidelines of the Canadian Council on Animal Care and were reviewed and approved by the institutional Animal Care Committee.

2.2. Drugs

(−)Nicotine hydrogen tartrate (Sigma–Aldrich, St. Louis, MO) was dissolved in saline, and the pH of the resulting solution was adjusted to 7.0 ± 0.2 before being filtered through a 0.22-mm syringe filter (Fisher Scientific, Pittsburgh, PA).

A mixture of baclofen and muscimol (0.3 and 0.03 nmol/side, respectively; Sigma-Aldrich) was dissolved in saline for intracranial infusions.

2.3. Initial operant training

Procedures were similar to those previously reported [14,17]. All operant procedures were conducted in experimental chambers with two retractable levers located on a chamber wall (Med Associates, St. Albans, VT). The start of each daily session was indicated by the extension of these two levers and the concurrent illumination of a house light on the opposing chamber wall. Over the course of 5 daily sessions, all rats were trained to press one of the two levers, the active lever, on a continuous reinforcement schedule in order to receive a 45 mg food pellet (Bio-Serv, Flemington, NJ) delivered to a receptacle positioned between the two levers. Responding on the opposite lever, the inactive lever, was recorded but had no consequences. Sessions concluded after rats had obtained 100 pellets or 60 min had passed, whichever occurred first.

2.4. Nicotine self-administration and reinstatement experiments

2.4.1. Jugular vein catheterization

Following the initial operant training period (Section 2.3), each rat was implanted with an intravenous catheter in the jugular vein exiting between the scapulae. Penicillin G (30,000 Units, SC) was given within 24 h before surgical procedures. Anesthesia was induced by a mixture of xylazine and ketamine hydrochloride (10 and 75 mg/kg, respectively, IP). Postsurgical analgesia was achieved using buprenorphine (0.01 mg/kg, SC). Animals recovered for a minimum of 7 days in their home cages.

2.4.2. Acquisition of nicotine self-administration

Operant chambers were similar to those described in section 2.3 with three major exceptions: (1) no food receptacle was present between the two levers, (2) the catheters described in section 2.4.1 were connected to a spring descending from the top of the chamber which was connected to a pump (Med Associates - Model PHM-104) allowing for reinforcement by rapid delivery (1 s infusion duration) of IV nicotine (0.03 mg/kg/infusion; free base concentration), and (3) a cue light was present above the active lever and would illuminate for the duration of the 60 s timeout period following each reinforcement during which time the house light was turned off and responding on either lever was recorded but had no consequences. Rats underwent 5 sessions of self-administration under a fixed-ratio 1 (FR-1) schedule of reinforcement, followed by 3 sessions under an FR-2 schedule and then 7 sessions under an FR-5 schedule (i.e. five active lever presses required for each reinforcement).

2.4.3. Intracranial cannulation

Following the acquisition of self-administration, rats underwent surgical implantation of bilateral microcannulae guide into the agranular insular cortex as follows. Rats were anaesthetised in an isoflurane (5%) induction chamber before being positioned in a stereotaxic apparatus (Kopf, Model 900) after which anaesthesia was maintained using isoflurane (1–2%) delivered via nose cone. The rats' heads were shaved and local anesthetic (0.1 ml bupivicaine, 0.125%) was injected at the incision site before betadine was applied to clean the area. An incision was made along the midline and the skull exposed. Location of bregma and lambda were determined and the skull was levelled. Sites of interest were determined relative to bregma as follows, RAIC: anteroposterior +2.8 mm, lateral ± 4.0 mm. Small holes were drilled at the respective sites for each rat. Guide microcannulae (22G; Plastics One, Roanoke, VA) were lowered 6.5 mm relative to the dorsoventral coordinate taken from the cranial surface at the site of interest. Guide cannulae were then fixed to the skull with screws and dental cement (Jet Set 4; Lang Dental, Wheeling, IL) and sealed with a stainless-steel occluder (Plastics One). Postsurgical analgesia was achieved using buprenorphine (0.01 mg/kg, SC). Rats were again given a minimum of 7 days recovery time in their home cages.

2.4.4. Cortical inactivation procedure

On testing days, injection cannulae were coupled to a 10 μL Hamilton syringe by a polyethylene tubing (inner diameter

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