BRAIN RESEARCH 1630 (2016) 64–72

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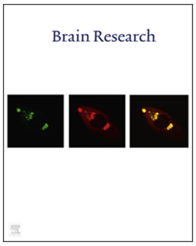

Research Report

Tolerance to repeated rewarding electrical stimulation of the insular cortex

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ARTICLE INFO

Article history:
Accepted 1 November 2015
Available online 10 November 2015

Keywords:
Place preference
Posterior agranular insular cortex
Decay and recovery of reinforcement

ABSTRACT

The insular cortex (IC) has been related to various reinforcing behavioral processes. This study examined the effect of electrical stimulation of the posterior agranular IC on concurrent place preferences. Two groups of animals and their respective controls underwent rewarding brain stimulation every day or on alternate days. While the rats stimulated every other day maintained their preference for the place associated with brain stimulation, those stimulated every day evidenced a reduction in their place preference, suggesting tolerance to the stimulation's rewarding effect. A 15% increase in the current intensity produced a recovery of the preferences of the daily-stimulated rats but had no effect on those stimulated on alternate days. These results are discussed in terms of the rewarding effects induced by different electrical and chemical rewarding agents.

1. Introduction

The insular cortex (IC) has been associated with different sensory, regulatory, and affective functions and with learning and memory, among other behavioral processes (Cechetto and Saper, 1987; Peyron et al., 2000; Shin et al., 2000; Zhang and Oppenheimer, 2000; Craig, 2002, 2009, 2010; Garavan, 2010; Ibañez et al., 2010; Purón-Sierra et al., 2010).

The IC is involved in taste discrimination processes (Cechetto and Saper, 1987; Zhang and Oppenheimer, 2000; Purón-Sierra et al., 2010; Maffei et al., 2012), possessing neurons sensitive to the hedonic properties of gustative stimuli (Maffei et al., 2012; Yamamoto et al., 1989; Shimura et al., 1995) and also to both innocuous and noxious somatosensory stimuli (Ogawa and Wang, 2002). It is also known to participate in regulatory processes associated with natural biological drives, including hunger, thirst, or sexual behaviors (Tataranni et al., 1999; Egan et al., 2003; Pelchat et al., 2004; Gizewski et al., 2006; Porubská et al., 2006; Safron et al., 2007; Hu et al., 2008; Zhu et al., 2010) and probably in general interoceptive functions (Craig, 2010; Naqvi and Bechara, 2009).

The IC is also reported to be involved in preference and aversive behaviors, suggesting that it may participate in the affective-emotional processing, integration, and evaluation of stimuli (Cechetto and Saper, 1987; Peyron et al., 2000; Zhang and Oppenheimer, 2000; Craig, 2002, 2009, 2010; Garavan,

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http://dx.doi.org/10.1016/j.brainres.2015.11.001
0006-8993/

2010; Ibañez et al., 2010; Mackey et al., 1986; Hanamori et al., 1998a, 1998b; Zhang et al., 1999; Cubero and Puerto, 2000; Sewards and Sewards, 2001; Sewards, 2004). This convergence function could derive from the different sensory afferents projecting to this region (Ibañez et al., 2010; Hanamori et al., 1998a, 1998b; Kimura et al., 2010) and from its connections with the limbic system (Morgane and Mokler, 2006) and caudal regions, including the parabrachial complex (Fulwiler and Saper, 1984; Bernard et al., 1991; Dobolyi et al., 2005). Thus, a strong correlation has been observed between insular activity and subjective reports related to feelings such as happiness, disgust, anxiety, sadness, or guilt (Shin et al., 2000; Liotti et al., 2000; Phan et al., 2002; Murphy et al., 2003; Marci et al., 2007; Stein et al., 2007; Cerqueira et al., 2008; Harrison et al., 2008; Takahashi et al., 2008).

The IC also participates in the learning of preference or aversive behaviors. Specifically, it has been confirmed that IC lesions impair the acquisition of taste aversions (Kiefer and Orr, 1992) and their retention after learning (Zito et al., 1988; Cubero et al., 1999). The IC has also been related to the processing of reward (De Couteau et al., 1997; Ragozzino and Kesner, 1999; Balleine and Dickinson, 2000; Elliott et al., 2000; Gottfried et al., 2003; Kirsch et al., 2003; Kesner and Gilbert, 2007). Thus, it has been shown that IC lesions impair recall of the magnitude of the rewarding value of foods (De Couteau et al., 1997; Ragozzino and Kesner, 1999; Balleine and Dickinson, 2000). The IC has been related not only to natural states but also to different drugs of abuse, especially to the craving induced by heroin, cocaine, nicotine, cannabis, or alcohol (Naqvi and Bechara, 2009; Wang et al., 1999; Sell et al., 2000; Brody et al., 2002; Tapert et al., 2004; Filbey et al., 2009). In this line, recent studies demonstrated that transient IC deactivation suppresses the impulse of addicted animals to seek and consume drugs of abuse, e.g., nicotine or amphetamines Contreras et al., 2007; Forget et al., 2010. Likewise, human tobacco addicts have been reported to discontinue the habit after a spontaneous insular lesion, with no signs of craving and no relapses (Naqvi et al., 2007).

Finally, electrical stimulation of the IC is known to induce preference behaviors for associated stimuli in taste discrimination learning and CPP tasks (Cubero and Puerto, 2000; García et al., 2013). In this regard, naloxone administration impairs CPP acquisition induced by electrical IC stimulation (García et al., 2013), consistent with the high density of opioid receptors in this region (Mansour et al., 1994; Svingos et al., 1995; Burkey et al., 1996; Izenwasser et al., 1999; Leppä et al., 2006) and its involvement in the processing of drugs of abuse, such as opiates (Mackey et al., 1986; Zito et al., 1988).

With this background, the objective of this study was to determine whether the repetition of IC stimulation reduces its rewarding effect in place preference tasks, as observed with other rewarding agents. If this proved to be the case, a further objective was to determine whether an increase in electrical current intensity counteracted this reduction in rewarding effect, as observed with some drugs of abuse.

2. Results

2.1. *Distribution of stimulated animals among groups*

The formation of the different groups and the distribution of stimulated animals depend on the time they stay in the maze compartment associated with electrical stimulation. The classification of stimulated animals into different groups was made according to the criteria used in previous studies in our laboratory (García et al., 2013): (a) "positive" animals, which consistently preferred the stimulated maze compartment and stayed for $>50\%$ of the time in this area; (b) "aversive" animals, which consistently avoided the stimulated compartment, staying in it for $<30\%$ of the time; and (c) "neutral" animals that evidenced no consistent preference or aversive behavior, staying for 30–50% of the time in the stimulated compartment. According to these criteria, we only selected the "positive" animals and "neutral" animals. The three "aversive" animals ($n=3$) observed were excluded from the study.

According to the aforementioned criteria and the results obtained in phase 1, the implanted group was divided into two groups: one formed by the animals that showed consistent preference for the compartment associated with the electrical IC stimulation (Positive Group, $n=16$), whose mean stay time in the stimulation-associated maze area 419.53 s.; and another group, including the rats that showed no preference for any maze areas (Implanted Neutral Group, $n=12$) and whose mean stay in the stimulated area was 239.50 s. From this time onwards, the latter animals became part of the neutral group and were used as control animals, receiving no further electrical stimulation in any of the subsequent experimental phases. Finally, the mean stay time in the stimulated maze area of the group of neurologically intact animals was 239.00 s.

The "positive" animals ($n=16$) were randomly divided into two groups: **Positive Group 1** and **Positive Group 2** ($n=8$ each). The implanted "neutral" animals were randomly assigned to one of two groups, Control Group 1 or Control Group 2, and the neurologically intact control animals were also randomly assigned to one of these groups. Finally, **Control Group 1** comprised 4 intact and 6 implanted neutral animals and **Control Group 2** comprised 5 intact and 6 implanted neutral animals.

2.2. *Repeated electrical stimulation*

After forming the four groups reported above (Positive Group 1; Positive Group 2; Control Group 1; Control Group 2), the results obtained in the different CPP sessions were analyzed

The statistical analysis of the data obtained during the 5 CPP sessions (baseline and repeated stimulating sessions) in each group was conducted by means of intra-group univariate analysis of variance (ANOVA). The results obtained for Positive Group 1 showed a significant effect of the CPP day factor ($F_{(4,28)}=5.27$; $p<0.0027$), (see Fig. 1), i.e., a reduction in the stay time of animals in the maze area associated with electrical IC stimulation. In contrast, the results obtained for