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Research report

Large neurotoxic amygdala lesion impairs reinforcement omission effects

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HIGHLIGHTS

- Amygdala is involved in the ROEs modulation.
- Lesions of the amygdala impair the ROEs.
- Amygdala lesion and ROEs: interference in anticipatory responses.
- ROEs can be driven by multiple processes.

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ABSTRACT

The amygdala has been implicated in a variety of motivational and attentional functions related to appetitive learning. Some studies showed that electrolytic lesions of the amygdaloid complex disrupted reinforcement omission effects (ROEs). However, recent studies that investigated ROEs employing neurotoxic lesions in specific amygdala areas – the central nucleus (CeA) or basolateral complex (BLA) of the amygdala – showed that CeA lesions or BLA lesions can interfere with, but do not eliminate ROEs. Although the effects of neurotoxic lesions in particular areas of the amygdala differed from those of a large gross lesion, these studies have indicated that it is possible that the amygdala is involved in ROE modulation. Furthermore, the effect that a neurotoxic lesion involving both areas (CeA and BLA) has on ROEs remains unexplored. Thus, the present study aimed to clarify whether the functional impairment related to large amygdala activation affects ROEs, in a neurotoxic lesion procedure. If this is the case, the underlying process may contribute to a better understanding of the involvement of the amygdala in ROEs modulation. After acquisition of stable performance during pre-lesion training in which rats were trained to respond on a fixed-interval 6 s with limited hold 6 s schedules (FI 6 s LH 6 s), lesions were made including both the CeA and BLA areas. In test sessions, the partial omission of reinforcement was introduced. The results showed that bilateral lesion of both CeA and BLA impaired ROEs, suggesting that amygdala is part of ROEs' modulation circuitry.

1. Introduction

Reinforcement omission effects (ROEs) have been attributed to motivational/emotional and attentional consequences of the unexpected omission of reinforcement. ROEs are empirically defined by the difference in response after omission relative to that following reinforcement. On the other hand, from a theoretical point of view, the response differences between after nonreinforcement and after reinforcement conditions can be driven by multiple processes [1]. One interpretation is in terms of frustration, evidenced by an increase in responses after nonreinforcement [2], and another in terms of transient behavioral inhibition after reinforcement induced by demotivation or the resetting of the internal clock [3,4]. Stout et al. [5] considered that ROEs are caused both by suppression after reinforcement and by facilitation after nonreinforcement, and that the extent to which each process contributes to ROEs is dependent upon the parameters of training.

Some studies have suggested that electrolytic lesions of the amygdala prevented ROEs [6–8]. Henke and Maxwell [8] showed that rats with lesions of the amygdala failed to alter running speeds

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in a runway when reinforcement was omitted from the first goal box of a double runway. Also, Henke [6] reported that rats with lesion of the amygdala, trained to respond on a fixed-interval (2 min) schedule, failed to increase response rates in intervals following nonreinforcement. As these studies produced amygdala lesions by radio frequency or electrolytic current, the elimination of the ROEs resulting from these techniques might be attributable either to extensive damage to the amygdala or to destruction of passage fibers [9]. Thus, recent studies have investigated the effect of selective amygdala lesions on ROEs by employing neurotoxic drugs to produce lesions. The role of the basolateral complex (BLA) and central nucleus (CeA) of the amygdala in the ROEs has been particularly explored [10–12] due to the assignment of attentional and motivational functions of these areas [13].

Recent evidence has shown that neurotoxic lesions of either the CeA or BLA can interfere with ROEs [10]. The results of Experiment 1 by Bueno [10] showed that rats with CeA or BLA lesions, trained to respond on a fixed-interval (FI 60 s) schedule, presented ROEs as well as rats of the sham-lesioned group. Furthermore, after nonreinforcement, there was no difference between the performances of the rats of either BLA or CeA lesioned groups and rats of the sham-lesioned group. However, the results of Experiment 2 indicated that BLA or CeA lesions can interfere with the ROEs when rats are trained to respond on a fixed-interval of 8 s with a limited hold of 2 s signaled schedule (FI 8 s LH 2 s). The rats of the group with CeA or BLA lesions and the rats of the sham-lesioned group presented ROEs: the response rates were higher following nonreinforcement than following reinforcement. However, after nonreinforcement, there were differences between the performances of the rats of both lesioned groups and rats of the sham-lesioned group: the response rates of the lesioned rats were lower than that of the sham-operated rats.

Although the effects of neurotoxic lesions in specific areas of the amygdala differed from those of a large gross lesion, studies have indicated that it is possible that the amygdala is involved in ROEs modulation. Furthermore, the effect of a neurotoxic lesion involving both areas (CeA and BLA) on ROEs remains unexplored. Thus, the present study is aimed to clarify whether functional impairment related to large amygdala activation affects ROEs, in a neurotoxic lesion procedure. If such is the case, the underlying process may contribute to the involvement of the amygdala in ROEs modulation. The lesions, including both the CeA and BLA, were induced after acquisition of pre-lesion training in which rats were trained to respond on a fixed- interval of 6 s with limited hold of 6 s schedules (FI 6 s LH 6 s). On a FI schedule with a limited-hold contingency (FI LH), reward is available for only a specified period of time after the FI terminates. Consequently, on a FI 6 s LH 6 s schedule, all responses occurring between 0 and 6 s after the start of the FI have no effect on reward; however, the first response occurring between 6 and 12 s is followed by a reward [1,11,12,16,18]. The schedule was presented with one stimulus and the correct responses were always followed by reinforcement (0.05 ml of water). In test sessions, the partial omission of reinforcement was introduced. The performance of the rats with BLA and CeA lesions (CeA/BLA group) and of the rats with sham lesion (Sham group) after reinforcement (R) and after nonreinforcement (N) was compared.

2. Materials and methods

2.1. Subjects

The subjects were 38 experimentally naive male Wistar rats (Central Vivarium at University of Sao Paulo at Ribeirao Preto), 90 days old at the beginning of the experiments, weighing from 416 g to 433 g. Throughout the experiments, the animals were housed in steel cages in the laboratory colony room, on a 12-hour light (lights on from 8:00 to 20:00). The rats were maintained on a water deprivation schedule at 85% of their ad libitum body weight by limiting access to water. Food was available at all times in their cages.

2.2. Surgical procedures

The animals were anesthetized by an intraperitoneal injection of a mixture containing 0.8 ml of ketamine hydrochloride (0.028 mg/ml) and 0.7 ml of xylazine (3.33 mg/ml). Each rat received 0.1 ml of anesthetic for each 100 g body mass. Bilateral neurotoxic lesions of the CeA and BLA (CeA/BLA group, $n = 22$) were made by injecting ibotenic acid (10 mg/ml in 0.1 M phosphate buffer with 0.9% saline) through a micropipette at the coordinates: CeA – 1.9 mm posterior to bregma and 4.5 mm from the midline, with infusions at a depth of 7.2 mm from the skull surface (0.25 μl per site); BLA – 2.8 mm posterior to bregma and 5.4 mm from the midline, with infusions at a depth of 8.0 mm (0.2 μl per site) and 7.7 mm (0.1 μl per site) from the skull surface. The ibotenic acid (Sigma) was infused with a Hamilton 5 μl syringe over a 2 min period. The Sham group ($n = 16$) received the same surgical treatment, with the exception that no solution was infused [10,11,14]. After surgery, all rats received a single subcutaneous injection of Banamine (2.15 mg/ml; 0.1 ml for each 100 g body mass) for amelioration of pain and were allowed to recover from the surgery for 5–7 days before behavioral testing.

2.3. Apparatus

The experiment was conducted in operant chambers (Lafayette model 80201) equipped with a speaker, which delivered a 1000 Hz, 30 dB tone; a 5 W house-light lamp; a retractable 5 cm lever. Each chamber was in a soundproof wooden box provided with a transparent acrylic window which was held in soundproof experimental rooms. An electrical interface (MRA-Electronic Equipment, Ribeirao Preto, Brazil) connected the experimental chambers to a PC. This system used a program prepared with Microsoft QuickBasic 4.0 designed for this experiment, which controlled the reinforcement mechanisms and registered and recorded lever presses.

2.4. Behavioural training procedures

2.4.1. Pre-training

Pre-training was carried out over two sessions. In the first session, each rat was trained to press the lever for one 0.05 ml drop of water. The following session consisted of continuous reinforcement training (CRF training). Each session lasted a maximum of 30 min.

2.4.2. Pre-lesion training

In the pre-lesion training (15 sessions), the rats were trained to respond on a fixed-interval 6 s with limited hold 6 s signaled schedules (FI 6 s LH 6 s). This schedule was presented simultaneously with a tone stimulus of 12 s: the first lever press occurred between 6 s and 12 s resulted in delivery of the 0.05 ml of water. All rats received 20 training trials per session; each trial was interpolated with variable intertrial intervals (ITI; mean: 75 s). At the end of each session, the rats were returned to their cages and given sufficient water to maintain their planned body weight schedule. The rats were water-deprived for approximately 23 h before the beginning of each session.

2.4.3. Post-lesion training

After recovery from surgery (approximately 1 week), the rats went through two refresher sessions. These sessions were the same ones as during the pre-lesion training.