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Increased brain glucocorticoid actions following social defeat in rats facilitates the long-term establishment of social subordination

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ABSTRACT

Social rank is frequently established through aggressive encounters between new conspecifics. Despite increasing evidence suggesting that social rank is critical for the well-being of both humans and animals, knowledge about the factors influencing social rank remain scarce. Stress was previously shown to affect the establishment and maintenance of social hierarchies in rats. Likewise, increasing systemic corticosterone levels post-encounter in the emerging subordinate rat facilitates the long-term establishment of social subordination. Here, we investigated whether central corticosterone actions are sufficient to mediate this effect. Our data shows that, indeed, an intracerebroventricular corticosterone injection given to the emerging subordinate rat facilitates the long-term maintenance of the subordinate rank. Next, we attempted to identify a particular brain region in which enhancement of corticosterone actions could be sufficient to exert the facilitation of a long-term maintenance in the emerging subordinate brain. However, post-encounter administration of corticosterone into the basolateral amygdala, medial amygdala, lateral septum and the nucleus accumbens, brain regions selected for their implication in social rank establishment and emotional modulation of memory, did not affect long-term social subordination. Our study highlights the involvement of intracerebral corticosterone actions on the facilitation of long-lasting subordinate behavior, likely by having a modulatory role in the neurobehavioral plasticity engaged in the shaping of social subordination.

1. Introduction

Most social animal species are arranged in dominance hierarchies [1], which follow the organizing principle that dominant animals have priority access to important resources. Social rank is frequently determined by intrinsic factors (e.g., body size, body weight), sometimes including rank inheritance from parents. However, in many occasions encounters with new conspecifics lead to a newly established rank [2]. Once settled, social hierarchies tend to be long-lasting [2]. Despite the great impact of rank for health and well-being in both animals and humans [3,4], information about the factors and mechanisms affecting the long-term establishment of social hierarchies is still scarce.

Using rat as model system, we have previously shown that when a pair of unfamiliar male rats competes for the establishment of a social hierarchy, acute stress experienced by one of the two rats just before their encounter substantially increases the probability that the stressed rat becomes subordinate [5]. As each pair of rats is matched for all possible intrinsic factors (i.e., age, body weight and size, anxiety levels, and previous life conditions), this observation allows to establish a causal role for stress on the resulting social order. Importantly, the impact of stress goes beyond the actual outcome of the first contest between the competing animals. Thus, while the hierarchical relationship established under non-stress conditions is not observed when the same two animals are confronted again one week afterwards, in those dyads, in which rank was set involving one stressed rat, the same rank is observed again [5]. Administration of a protein synthesis inhibitor interfered with this potentiation of memory by stress, suggesting that a 'memory consolidation' process is involved in the long-term facilitation of the maintenance of the social hierarchy by stress [5].

Given that glucocorticoids, end products of the activated hypothalamus-pituitary-adrenal (HPA) axis, are activated by social encounters [6,7], elevated glucocorticoid levels at the time of a first social encounter between two individuals were hypothesized to affect the long-term establishment of social rank [8]. This hypothesis was based on two lines of evidence regarding glucocorticoid actions in brain and behavior. The first one relates to the ability of glucocorticoids to exert rapid, non-genomic effects in specific cell types and brain regions [9,10] swiftly resulting in behavioral activation [11–13] and enhancing

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aggression in ongoing contests [14]. The second one relates to a long-standing literature linking post-experience glucocorticoids with the facilitation of long-term memory [for reviews, see [15–18]]. Accordingly, our previous work showed that whereas systemic corticosterone treatment given to one of the two rat contenders before a first social encounter does not affect the outcome of the social hierarchy during a first encounter, it modified ongoing behavioral interactions when the injected male was the one that won dominance from the encounter [8]. However, the strongest effect was observed in the case when the subordinate rat received a systemic corticosterone injection immediately after the first social encounter. This treatment led to a long-lasting maintenance of the acquired social hierarchy [8], mimicking previously reported actions of stress in the same model [19]. In contrast, no long-term impact was observed when the dominant animal was the one that received the treatment [8]. Importantly, cumulative evidence in the literature indicates that once dominance relationships are established, plasma corticosterone swiftly normalize in the winner, while continuing elevated in the loser [[20–22]; for review, see [23]]. A key question arising from the findings implicating an enduring facilitation of the acquired subordination status by increasing post-encounter plasma corticosterone levels [8] is whether the effect could result from the central action of glucocorticoids.

Here, we asked whether we could exclude the necessity of peripheral glucocorticoid actions to account for the long-term facilitation of social subordination and, conversely, establish the sufficiency of brain corticosterone actions to induce this effect. To this end, we set a study to investigate whether intracerebroventricular (i.c.v.) administration of corticosterone to the animal emerging as subordinate out of a first dyadic contest would potentiate the long-term maintenance of the subordinate rank as well. As a secondary goal, we set to ask whether we could identify one specific region that would account for the corticosterone effect. Specifically, we performed experiments to assess whether post-encounter administration of corticosterone into specific brain regions selected for their implication in social rank establishment and emotional modulation of memory (i.e., basolateral and medial amygdala nuclei, lateral septum and nucleus accumbens) would be able to facilitate long-term maintenance of subordination.

2. Results

2.1. Post-encounter intracerebroventricular administration of corticosterone facilitated the long-term maintenance of social subordination

Animals of each dyad underwent a first social encounter consisting of a social interaction test followed by a food competition test. Immediately afterwards, the loser animal received an i.c.v. infusion of corticosterone [10 μg/3 μl; dose selected based on previously published work [24]], while the dominant animal was infused with vehicle (Fig. 1A). After one week in which both animals were housed separately, the very same dyads were reunited in a neutral home cage and given a water competition test to assess for the maintenance of the social rank established during the first social encounter (Fig. 1A).

As expected, in vehicle-injected rats the social hierarchy established on day 1 was not maintained across days ($t(5) = 0.075$, $p = 0.94$; Fig. 1B). However, the dyads in which the subordinate animal was i.c.v.-infused with corticosterone after the first social encounter had the very same animals showing subordinate behavior during the water competition test ($t(6) = 3.084$, $p = 0.02$; Fig. 1C). Thus, i.c.v. corticosterone infusion in recently defeated rats facilitated the transition of social subordination established at day 1 to its maintenance on day 8. These results indicate that corticosterone actions in the brain are crucially involved in the facilitation of a long-term memory of social subordination in rats.

2.2. Post-encounter administration of corticosterone into specific brain regions did not affect long-term social subordination

After observing that corticosterone actions in the brain are crucial for the formation of a long-term social memory in rats, we next tried to identify a particular brain region in which enhancement of corticosterone actions could be sufficient to exert the effect. We selected a few key brain areas known to play important roles in memory modulation and/or social behavior, including the basolateral amygdala, medial amygdala, lateral septum and nucleus accumbens. We applied the same experimental set-up as before with dominant animals receiving post-encounter infusion of vehicle and subordinate animals receiving post-counter infusion of corticosterone into the here examined brain regions (Fig. 2A).

The first brain area of interest was the basolateral amygdala which has been described to play a role for memory modulation by glucocorticoids [16] and aggressiveness in social encounters in rats [25]. Thus, we assessed the long-term impact of intra-basolateral amygdala corticosterone infusions in social subordination. However, our results showed that initially subordinate animals on day 1 did not behave subordinate on day 8, but had equal chances to become dominant or subordinate during the second social encounter ($t(16) = 1.036$, $p = 0.32$; Fig. 2B). Thus, we did not confirm a potential role for the basolateral amygdala on the corticosterone-induced enhancement of a long-term social subordination.

Then, we tested the potential efficiency of corticosterone infusions into the medial amygdala, as this brain region has been implicated in social behaviors and dominance hierarchies [16,26–28]. However, intra-medial amygdala infusion of corticosterone of subordinate animals failed as well to facilitate long-term social subordination in the

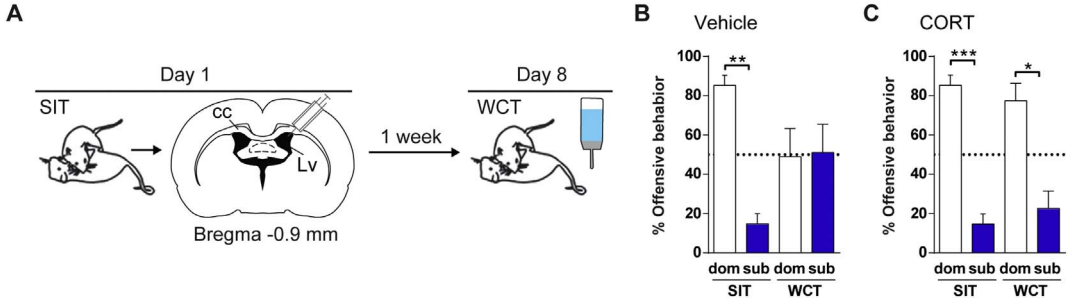

Fig. 1. Post-encounter intracerebroventricular administration of corticosterone.
(A) Schematic representation of the experimental protocol. Day 1: First social encounter consisting of a 20 min social interaction test (SIT) followed by intracerebroventricular (i.c.v) infusion to each animal of a dyad. Vehicle (saline) into dominant animals and corticosterone (CORT) into subordinate animals. Day 8: Second social encounter consisting of a 10 min water competition test (WCT) to test for social memory. Images of brain sections were adapted from the rat brain atlas [53]. (B, C) The percentage of total offensive behavior (mean S.E.M.) between two opponents shown in SIT on day 1 and the WCT on day 8 in the post-social encounter injection groups. Post-social encounter vehicle for dominant, post-social encounter CORT for subordinate rat. (B) i.c.v.-infusion of vehicle (saline) (n = 6). (C) i.c.v.-infusion of 10 μg/3 μl CORT (n = 7). The status 'dom' (dominant) or 'sub' (subordinate) in the WCT refers to the status that was obtained during the SIT on day 1. Abbreviations: cc, corpus callosum; Lv, lateral ventricle. *$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$.

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