Published in final edited form as:

Behav Brain Res. 2015 June 1; 286: 22–28. doi:10.1016/j.bbr.2015.02.030.

Dopamine in the nucleus accumbens modulates the memory of social defeat in Syrian hamsters (*Mesocricetus auratus*)

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Abstract

Conditioned defeat (CD) is a behavioral response that occurs in Syrian hamsters after they experience social defeat. Subsequently, defeated hamsters no longer produce territorial aggression but instead exhibit heightened levels of avoidance and submission, even when confronted with a smaller, non-aggressive intruder. Dopamine in the nucleus accumbens is hypothesized to act as a signal of salience for both rewarding and aversive stimuli to promote memory formation and appropriate behavioral responses to significant events. The purpose of the present study was to test the hypothesis that dopamine in the nucleus accumbens modulates the acquisition and expression of behavioral responses to social defeat. In Exp. 1, bilateral infusion of the non-specific D1/D2 receptor antagonist cis(z)flupenthixol (3.75 µg/150 nl saline) into the nucleus accumbens 5 min prior to defeat training significantly reduced submissive and defensive behavior expressed 24 hr later in response to a non-aggressive intruder. In Exp. 2, infusion of 3.75 µg cis(z)flupenthixol 5 min before conditioned defeat testing with a non-aggressive intruder significantly increased aggressive behavior in drug-infused subjects. In Exp. 3, we found that the effect of cis(z)flupenthixol on aggression was specific to defeated animals as infusion of drug into the nucleus accumbens of non-defeated animals did not significantly alter their behavior in response to a non-aggressive intruder. These data demonstrate that dopamine in the nucleus accumbens modulates both acquisition and expression of social stress-induced behavioral changes and suggest that the nucleus accumbens plays an important role in the suppression of aggression that is observed after social defeat.

Keywords

CONDITIONED DEFEAT; FEAR LEARNING; SOCIAL STRESS; AGGRESSION

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Conflict of interest

The authors have no conflict of interest.

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Introduction

Social stress is one of the most common stressors that humans face, and stressors such as bullying and workplace harassment can cause or exacerbate post-traumatic stress disorder [1], social or generalized anxiety disorder [2], schizophrenia [3, 4] and depression [5]. We have a relatively poor understanding, however, of the mechanisms whereby social stress causes changes in brain and behavior (e.g., increases in social avoidance, generalization of fear, and changes in aggression). An improved understanding of these mechanisms is critical for finding new treatment options for these debilitating conditions.

The Syrian hamster is an ideal species with which to study the neurobiology of social stress because these animals display a pronounced behavioral response to social defeat, which we term conditioned defeat. Instead of producing the species-typical territorial aggression toward a novel conspecific, a hamster that has been defeated generally exhibits submissive and defensive behavior and little to no aggression toward an intruder placed in its home cage. Even a smaller, non-aggressive opponent triggers this generalized fear response. This indiscriminate avoidance may be analogous to the generalized fear exhibited by sufferers of PTSD. Interestingly, conditioned defeat is observed in both male and female hamsters, though the response to social defeat in females is dependent on the phase of the estrus cycle on the day of testing [6].

We have begun to define the neural circuit underlying the acquisition (learning and memory of the initial defeat experience) and the expression (production of avoidance and submissive behavior displayed in response to the presence of a non-aggressive intruder) of conditioned defeat. Activation of GABA_A receptors [7] or blockade of NMDA receptors [8] in the basolateral amygdala (BLA) block both acquisition and expression of this response, while viral vector-mediated overexpression of cyclic AMP response element binding protein in the BLA enhances conditioned defeat learning following a very short exposure to social stress [9]. Finally, the BLA appears to be the sole region tested thus far wherein protein synthesis is necessary for acquisition of conditioned defeat [10]. Though more work is clearly needed to fully illuminate this question, at the very least, the data indicate that the BLA is a critical region where the memory of social defeat is ‘crystallized’ and goes on to influence ongoing agonistic behavior.

We have previously demonstrated that GABA_A receptor activation within the nucleus accumbens decreases the expression, but not the acquisition, of conditioned defeat [11], suggesting that the nucleus accumbens (NAcc) promotes submissive behavior following defeat but is not necessary for the formation of the memory of that defeat. Use of GABA_A receptor agonists to “temporarily” or “reversibly” inactivate a brain region is a commonly used tool and may be particularly effective in brain regions, such as the BLA, which express GABAergic interneurons that are known to play a critical role in controlling overall excitability of that brain area [12, 13]. Recent findings, however, indicate that there are distinct actions of GABA and dopamine within the nucleus accumbens, whereby dopamine acts on processes mediating long-term potentiation, but GABA does not [14]. This suggests that our previous conclusion that the nucleus accumbens does not modulate the acquisition of conditioned defeat may have been erroneous.

Dopamine is a neurotransmitter of particular interest for study of the neurobiological mechanisms underlying behavioral responses to social stress because dopaminergic dysregulation has been associated with such disorders as schizophrenia [3, 15] and post-traumatic stress disorder [16, 17]. The main source of dopamine to limbic regions of the brain, such as the nucleus accumbens, amygdala and infralimbic cortex, is the ventral tegmental area [18]. Physical stress [19] and chronic social stress [20, 21] increase phasic firing of VTA dopaminergic neurons, likely through the action of corticotropin releasing factor released during exposure to the stressor [22, 23]. Dopamine has also been implicated in the expression of social avoidance after chronic defeat in mice [24], and social stress increases dopamine in the nucleus accumbens [25]. However, no one has examined whether dopamine within the nucleus accumbens is necessary for the formation of a memory for a social defeat or for the expression of behavioral responses following an acute social defeat.

The general consensus in the literature is that dopamine gates excitation to allow the most salient stimuli [26, 27], both rewarding and aversive, to be remembered and to change future behavior. The evidence that dopamine can enhance both memory formation and neural activation within the nucleus accumbens suggests that dopamine might be necessary for long-term potentiation and neuronal activation of the nucleus accumbens during and after an acute social defeat experience. Thus, the purpose of this study was to test the hypothesis that dopamine in the nucleus accumbens modulates the memory of a social defeat as well as the expression of behavioral responses to acute social defeat in Syrian hamsters.

Methods

2.1. Animals

Subjects were adult male Syrian hamsters (*Mesocricetus auratus*; Charles Rivers Laboratories, Wilmington, MA) that weighed 120–130 grams upon arrival and were about 9 weeks old at the time of testing. All subjects were individually housed for at least one week prior to the start of testing in a temperature ($20 \pm 2^\circ\text{C}$) and humidity-controlled room with *ad libitum* access to food and water. Subjects were weight-matched and randomly assigned to their drug groups. Animals were kept on a 14:10 light:dark cycle (lights out at 10:00 h). Resident aggressors (RA) used for defeat training were older (> 6 mo), singly housed males weighing between 160 and 180 g. Younger males (~ 2 mo) that weighed between 100 and 110 g were group-housed (four to five per cage) and were used as non-aggressive intruders. The cages of the subjects and the resident aggressors were not changed for 1 week prior to testing so that animals could scent mark their cages and establish residency. All procedures and protocols were approved by the Georgia State University Institutional Care and Use Committee and conform to PHS guidelines.

2.2. Surgical procedures

Subjects were anesthetized via exposure to 5% isoflurane mixed with oxygen, placed into a stereotaxic frame, and maintained under anesthesia via a nose cone that delivered 2–3% isoflurane. The animal was then administered 5 mg/kg ketofen and 1 ml 0.9% saline to provide pain relief and fluids, respectively. Bregma and lambda were leveled, and then stainless steel guide cannulae (26-gauge, 4.0 mm long below the pedestal) were implanted

bilaterally into the brain aimed at the nucleus accumbens (2.0 mm rostral, $\pm$ 3.2 mm from bregma and at a 20° angle toward the midline). To avoid damage to the area of interest, the guide cannula was lowered 2.7 mm below dura. On the day of injection, a 33-gauge injection needle was used that projected 2.3 mm below the guide cannula, reaching a final depth of 5 mm below dura. After guide cannulae implantation, a wound clip was placed in the skull caudal to the guide cannulae as an anchor and then dental cement was used to secure the cannulae and clip to the skull. Following surgery, dummy stylets were placed in the cannulae to help maintain patency. Hamsters were allowed 7–10 days to recover from surgery prior to the start of behavioral testing. Beginning 2 days after surgery, the hamsters were handled each day by gently restraining them and removing and then replacing the dummy stylets in order to maintain cannula patency and to habituate the subjects to the injection procedure.

2.3 Behavioral procedures

The conditioned defeat model has been extensively described elsewhere [28]. Briefly, on the day of social defeat training, animals were transported to the testing suite within the vivarium and allowed to acclimate to the environment for 1 h. All training and testing sessions were performed under dim red illumination during the first 3 h of the dark phase of the light–dark cycle to reduce circadian variation in behavior [29]. Training consisted of one 15-min exposure to the RA in the aggressor's home cage, upon which time the RA reliably attacked the subjects within 60 sec. The following day, animals were again transported to the testing suite, and an NAI was placed into the subject's home cage for 5 min. All training and testing sessions were videotaped via a CCD camera mounted overhead. These videos were scored by an observer that was blind to treatment group using the behavioral scoring program Noldus ObserverPro. A second observer scored a random subset of these videos. Inter-rater reliability (i.e., percent agreement) between the two observers was above 90%. The total duration of four classes of behavior were measured during the test session: (1) social behavior (stretch, approach, sniff, nose touching, and flank marking); (2) non-social behavior (locomotion, exploration, grooming, nesting, feeding, and sleeping); (3) submissive/defensive behavior (flight, avoidance, tail up, upright, side defense, full submissive posture, stretch attend, head flag, attempted escape from cage); and (4) aggressive behavior (upright and side offense, chase and attack, including bites).

2.4. Drugs

Because both D1 and D2 receptors are implicated in Pavlovian fear conditioning [30–32], we elected to use cis(z)flupenthixol (Sigma), a non-specific D₁/D₂ receptor antagonist, to block both D1 and D2 receptors in the nucleus accumbens. This drug was administered bilaterally at a concentration of 0.0, 3.75 (8.55 nmol) or 15 μ g (34.5 nmol) in 150 nl saline (the highest dose was used only to test the effect of cis(z)flupenthixol on acquisition of conditioned defeat). These dosages were taken from previous literature [33] indicating the effective dose of cis(z)flupenthixol in the nucleus accumbens. This volume of drug or vehicle was also infused into the nucleus accumbens in a previous study in our lab [11].

2.5. Injection procedures

Drug or vehicle was infused bilaterally into the nucleus accumbens over a 1-minute period using a 1- μ l syringe and a PHD 2000 Harvard Apparatus microinfusion pump connected to a 33-gauge injection needle via polyethylene tubing. The needle was kept in place for an additional minute before removal to ensure diffusion of the drug or vehicle away from the injection site, after which the dummy stylet was replaced. A successful injection was indicated by movement of an air bubble separating drug and water down the tubing and/or patency of the needle before and after the injection. Training or testing began 5 minutes after drug or vehicle infusion.

2.6. Site verification

After testing, animals were sacrificed with an overdose of sodium pentobarbital and 150 nl of India ink was injected in each cannula to verify injection placement. Brains were post-fixed in 10% buffered formalin for at least 3 days before sectioning on the cryostat. 30 μ m sections were collected, stained with neutral red and cover slipped with DPX. An observer blind to experimental condition examined the sections with a light microscope for verification of injection sites. Animals in the drug groups were excluded if the injection was more than 300 μ m outside of the border of the nucleus accumbens, but all saline animals were included so as to reduce the number of total animals in the study (see histology in results section).

2.7. Experiment 1: Role of dopamine receptor activation in the nucleus accumbens in the acquisition of conditioned defeat

The goal of this experiment was to determine whether dopamine receptor blockade within the nucleus accumbens using the D₁/D₂ receptor antagonist cis(z)flupenthixol reduces the acquisition of conditioned defeat as evidenced by an increase in submissive/defensive behavior and/or a decrease in aggression in previously defeated hamsters. Hamsters received drug (3.75 or 15 μ g) or vehicle infusion 5 min prior to being placed into the home cage of a resident aggressor for 15 minutes for defeat training. On the following day, animals were tested drug-free in their own cage against a non-aggressive intruder for 5 minutes.

2.8. Experiment 2: Role of dopamine receptor activation in the nucleus accumbens in the expression of conditioned defeat

The goal of this experiment was to determine whether dopamine receptor blockade within the nucleus accumbens during testing reduces the expression of conditioned defeat in response to the non-aggressive intruder. In Experiment 1, we determined that the effective dose of cis(z)flupenthixol in the nucleus accumbens was 3.75 μ g, so only this dose or vehicle was used for Experiment 2. Hamsters were placed drug-free in the home cage of a resident aggressor for 15 min of defeat training. Animals were given the infusion 24 hours later into the nucleus accumbens 5 minutes prior to the 5-minute test with the NAI.

2.9. Experiment 3: Does cis(z)flupenthixol alter aggressive behavior in non-defeated hamsters?

The goal of the final experiment was to determine if the effect of 3.75 µg cis(z)flupenthixol on expression of conditioned defeat observed in Experiment 2 is specific only to defeated animals and/or if the drug also promotes aggression in non-defeated animals. Stereotaxic surgery to implant cannula guides was performed as described previously. Following recovery, subjects were placed in the empty cage of a resident aggressor for 15 minutes as a control for the effect of exposure to a novel conspecific's cage. On the following day, subjects were administered either 3.75 µg cis(z)flupenthixol or vehicle 5 minutes prior to a 5-minute test with an NAI.

2.10. Statistics

One-way ANOVAs or t-tests were performed, as appropriate. If homogeneity of variance was violated, a Kruskal-Wallis or Mann-Whitney U non-parametric test was run. Statistical significance for all tests was set at $p < 0.05$.

Results

3.1 Dopaminergic receptor activation is necessary in the nucleus accumbens for the acquisition of conditioned defeat

3.1.1. Histology—The behavior exhibited by animals in the saline group was not statistically different if the injection site was determined to be an anatomical hit ($n = 4$) or miss ($n = 5$), so the behavioral data for these two groups were pooled in order to reduce the number of animals that were required (data not shown). There were only 2 animals from the 3.75 µg dose group and 2 animals from the 15 µg dose group that had cannulae placements that were either bilateral or unilateral anatomical misses. Only animals that received cis(z)flupenthixol and were bilateral anatomical hits (defined as cannulae placements within 300 µm of the nucleus accumbens) were included in the main statistical analysis (see behavioral results for discussion of the behavior of animals with anatomical misses). Localization of injection sites are shown in Figure 1.

3.1.2. Behavioral results—As shown in Figure 2, an infusion of 3.75 µg cis(z) into the nucleus accumbens significantly decreased the duration of submission as compared to vehicle controls ($H(2)=6.284$, $p < 0.05$) in Experiment 1. There were no other significant differences among the three drug groups for any other behavior. There were also no significant differences in the duration of aggression expressed by the resident aggressor toward the subjects that received an infusion of vehicle or 3.75 µg cis(z)flupenthixol (with a mean duration of 275.75 ± 44.1 sec and 438.9 ± 97 sec, respectively) or in the duration of submission displayed by the subjects (with a mean duration of 406 ± 32.5 sec for vehicle-infused animals and 511 ± 81 sec for 3.75 µg-infused animals), indicating that cis(z)flupenthixol did not significantly influence the behavior of resident aggressors or subjects during defeat training. It is important to note that the apparent, although non-significant, increase in aggression directed towards drug animals by the RAs did not offset the drug-induced suppression of submission during testing, emphasizing the effectiveness of this drug in reducing the acquisition of conditioned defeat. In addition, this apparent increase

in aggression from the RAs was mirrored by a concomitant increase in submission by the subjects, indicating that these drug-treated animals are capable of producing appropriate submissive behaviors when attacked.

Of the four animals that were “anatomical misses” (2 received 3.75 µg and 2 received 15 µg cis(z)flupenthixol), each of these animals actually had a unilateral placement in the nucleus accumbens and one placement 300 µm or more from the accumbens. The two animals receiving 3.75 µg drug exhibited 1 ± 1 sec submission and the two animals receiving 15 µg cis(z)flupenthixol displayed 41.5 ± 41 sec submission. Thus, the animals receiving unilateral drug injections displayed behavior that was statistically similar to that displayed by animals receiving bilateral drug injections.

3.2. Defeat-induced suppression of aggression is mediated, at least in part, by activation of dopamine receptors

3.2.1 Histology—Locations of microinjections from Experiment 2 are also shown in Figure 1. There were no significant behavioral differences in the vehicle group between animals whose cannulae were determined to be anatomical hits ($n = 5$) or misses ($n = 5$), so the behavioral data for all vehicle animals were pooled. In the 3.75 µg drug group there were enough animals with anatomical misses to compare hits ($n = 5$) and misses ($n = 4$). Animals that had an infusion of 3.75 µg cis(z)flupenthixol into the nucleus accumbens exhibited a significant increase in aggression as compared to both vehicle control and anatomical drug misses (see Figure 3).

3.2.2. Behavioral results—As shown in Figure 3, the duration of submission expressed by animals in the vehicle control group was too low to see any effect of the drug on submission in Experiment 2. Cis(z)flupenthixol infusion, however, significantly increased aggression ($U = 9.0$, $p < 0.05$) in those animals with bilateral hits into the nucleus accumbens as compared with aggression displayed by animals receiving vehicle or by animals that were included in the anatomical miss control group for 3.75 µg cis(z)flupenthixol. Cis(z)flupenthixol infusion also decreased social behavior ($F(2, 16) = 9.176$, $p < 0.01$) as compared to vehicle.

3.3 Cis(z)flupenthixol does not alter agonistic behavior in non-defeated hamsters

3.3.1. Histology—There were no significant differences in any behavior between animals in the saline control group that were anatomical hits ($n = 5$) versus misses ($n = 3$) and so their data were pooled (data not shown). There were 6 drug animals with bilateral anatomical hits and no anatomical miss controls.

3.3.2. Behavioral results—As shown in Figure 4, there were no significant behavioral differences in Experiment 3 between non-defeated animals that received a microinjection of vehicle and those that received a 3.75 µg dose of cis(z)flupenthixol in the nucleus accumbens. Thus, there is no indication that the drug directly increases aggression.

Discussion

These experiments demonstrate that infusion of the non-specific D₁/D₂ dopamine receptor antagonist cis(z)flupenthixol into the nucleus accumbens reduces the acquisition of conditioned defeat in Syrian hamsters. It is unclear if dopamine receptor activation is necessary for the full expression of conditioned defeat, as animals in the vehicle control group in this particular experiment produced too little submission to observe an effect of the drug on submissive behavior after defeat. However, there was a significant increase in the duration of aggression in defeated hamsters that received drug. Together, the findings indicate that dopamine receptor activation in the nucleus accumbens modulates both the acquisition and expression of behavioral responses to social defeat. These findings are particularly notable because 1) we previously thought that the nucleus accumbens was not involved in the acquisition of conditioned defeat and 2) we have not previously identified brain regions that may selectively mediate defeat-induced suppression of aggression (note that we previously found that the lateral septum non-selectively modulates the expression of aggression in both non-defeated and defeated hamsters [35]).

Dopamine in the nucleus accumbens is predominantly thought of as a neurochemical signal that modulates reward-related processes [33, 36–38], so the finding that dopaminergic receptor blockade during defeat training decreases subsequent conditioned defeat is one of the first to demonstrate a role for dopamine in the formation of an aversive social memory following acute social stress. Previous research has demonstrated that the nucleus accumbens modulates classical fear memory [39, 40] and that dopaminergic receptor blockade within the nucleus accumbens reduces the memory of a conditioned taste aversion [41]. Our results are also consistent with recent studies indicating that dopamine is necessary for expression of social defeat-induced behavioral changes following chronic defeat [24, 42] (but see also [43]). This is the first study, however, to link dopaminergic receptor antagonism during the initial social defeat to a blockade of subsequent behavioral changes. Other social stress studies have examined dopamine in the brain during defeat using microdialysis [25] or fast-scan cyclic voltammetry [20], but they have not tested the role of dopamine in memory modulation in response to social defeat.

The current data provide additional clues to the mechanism whereby the nucleus accumbens modulates the acquisition of conditioned defeat. We had previously concluded that the nucleus accumbens did not play a role in the acquisition of conditioned defeat because infusion of a GABA_A receptor agonist, which is generally thought to temporarily inactivate the injected site, did not alter conditioned defeat. The current study, however, demonstrates that dopamine receptor activation within the nucleus accumbens is necessary for the full behavioral response to an acute social defeat experience. These conflicting findings can perhaps be explained by a recent study [14], which demonstrated that dopamine regulates LTP in neurons within the NAcc while GABA does not. Future studies should determine if other brain regions, including the lateral septum, previously thought to affect only expression of behavioral responses to social defeat do indeed modulate the initial learning of the behavioral responses to social defeat through the activation of dopaminergic receptors. The lateral septum is especially of interest because it is also necessary for the expression of

aggression by Syrian hamsters [35], and there is some evidence of dopaminergic effects on fear memory within the septum [44–46].

We cannot at this time determine if dopamine receptor activation in the NAcc is necessary for the expression of submissive and defensive behavior after defeat because of the low submission observed in the second experiment. The low level of submission demonstrated by controls in this experiment can most likely be attributed to the natural variance sometimes observed in our naturalistic model of social stress. We did find, however, that dopamine receptor blockade within the nucleus accumbens increases aggression produced by defeated animals, and given that this was specific to defeated hamsters and not non-defeated animals, we can rule out a generalized stimulation of aggression due to this treatment. The demonstration that manipulations of neurochemical signaling within the nucleus accumbens can enhance aggressive behavior following social defeat is very interesting and warrants further study. There is a previous study indicating that there is increased dopamine in the nucleus accumbens of hamsters demonstrating the winner effect, that is, increased aggression after repeated successful agonistic encounters [47]. It is intriguing that in defeated hamsters dopaminergic receptor blockade within the nucleus accumbens also increases aggression. Together, these data suggest a general role for dopamine in the nucleus accumbens in the formation of experience-induced changes in agonistic behavior. This dual role for dopamine in winning and losing is also consistent with the argument that dopamine acts as a signal of salience [48, 49], enhancing the memory of important events and altering behavior accordingly regardless of its valence. In other components of the neural circuit mediating conditioned defeat, we have shown that various manipulations are effective in significantly altering submission, but not aggression [7, 10, 50, 51]. Thus, we have been able to identify where memories of social defeat that promote submission can be inhibited but not those that inhibit aggression. This study indicates that the latter memory formation may depend, at least in part, on dopamine the nucleus accumbens. We have previously inhibited protein synthesis (a necessary component of long-term potentiation) in the amygdala using anisomycin and have demonstrated that the BLA is the one region where the synaptic plasticity necessary for an increase in submission occurs. Future studies could determine if the nucleus accumbens is the region where the necessary synaptic plasticity underlying the inhibition of aggression occurs by infusing anisomycin in the nucleus accumbens prior to defeat

There is strong evidence to suggest that the core and shell of the nucleus accumbens have separate and distinct roles with the core modulating reward and addiction [33, 52–55] and the shell modulating fear or aversion [49, 56, 57]. There are also indications that these different roles stem from the specific projections of the core and shell to different areas of the brain, with the shell projecting primarily to limbic regions often characterized as the central extended amygdala, while the core projects to striatal areas and lateral hypothalamus [58]. Unfortunately, the and microinjection volume given in the current study probably does not selectively reach one subdivision of the nucleus accumbens. Further studies are needed to address whether the effects observed here are primarily due to drug actions in the accumbens shell.

Given that cis(z)flupenthixol has a relatively long half-life in plasma when given orally or intravenously [59], it is possible that the levels of cis(z) in the brain were still high enough to affect expression of social defeat-induced behavioral changes 24 hours after defeat. Given the fact that the effect of the drug given before testing (i.e., an increase in aggression) was not observed following pre-training injections, however, it is highly unlikely that drug given before defeat training was still active during testing 24 hr later. Cis(z)flupenthixol is also an antagonist of both D1 and D2 receptors, though it has a higher affinity for the D1 than the D2 receptor [60]. Future studies should use specific D1 and D2 receptor antagonists, such as SCH-23390 and raclopride, respectively, to determine which receptor subtype is responsible for the effect of cis(z)flupenthixol on acquisition and expression of behavioral responses to social defeat. This would also have the added benefit that the specific receptor antagonists have a shorter half-life compared to cis(z)flupenthixol [61, 62]. We hypothesize, given that activation of D1 receptors increases adenylyl cyclase [63] which is critical for long-term potentiation and memory [64], that the D1 receptor is likely responsible for the effect of cis(z)flupenthixol on memory of social defeat. It may also be that the higher 15 µg dose of cis(z)flupenthixol used in Experiment 1 resulted in maximal binding at D1 receptors. Therefore, at this dose, the drug binds more at D2 receptors, which could then counteract to some extent the reduction in submission observed at the lower drug dose [26, 65].

In summary, the present findings indicate that dopaminergic receptor activation in the nucleus accumbens promotes the acquisition of behavioral changes following social defeat in Syrian hamsters. It is also evident that dopamine in the nucleus accumbens modulates aggressive and social behavior during expression of conditioned defeat. We should note that our results provide an interesting addendum to a previous study demonstrating that GABA_A receptor activation decreases expression, but not acquisition, of conditioned defeat. It seems that dopamine in the NAcc can indeed alter the acquisition of the memory of social defeat in Syrian hamsters, whereas neuronal inhibition via GABA_A receptor activation only decreases expression of behavioral responses to social defeat. Finally, the finding that dopamine within the nucleus accumbens modulates the learning and memory of behavioral responses to social defeat suggests that treatment with dopamine receptor antagonists might be clinically useful following exposure to traumatic events [15, 17, 66, 67].

Acknowledgments

Supported by NIH MH62044 to KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Highlights

- Dopamine in the NAcc modulates the acquisition/expression of conditioned defeat.
- GABA and dopamine in the NAcc differentially modulate the memory of social defeat.
- Dopamine modulates aggression in previously defeated hamsters.

Figure 1.

Histological reconstruction of cis(z) injection sites for acquisition (A) and expression (B) experiments. All symbols indicate the location of one or more cannula placements. Circles indicate vehicle doses, squares indicate 3.75 µg doses of cis(z)flupenthixol, and triangles indicate 15 µg doses of cis(z). Open symbols indicate hits and closed symbols indicate misses. A. Histological reconstruction of injection sites in animals that received vehicle, 3.75 µg or 15 µg cis(z)flupenthixol prior to defeat training. B. Histological reconstruction of injection sites in animals that received vehicle or 3.75 µg cis(z)flupenthixol prior to conditioned defeat testing. Drawings adapted from [34].

Figure 2.

Cis(z)flupenthixol infusion into the nucleus accumbens reduces the acquisition of conditioned defeat. Animals received infusions of drug or vehicle 5 minutes prior to being defeated by a resident aggressor for 15 minutes. Bar graph shows the total duration (mean $\pm$ SEM) in sec of submissive/defensive, aggressive, social and nonsocial behavior exhibited by defeated hamsters during a 5-minute test on the following day. *Significantly different from vehicle control ($p < 0.05$).

Figure 3.

Cis(z)flupenthixol infusion into the nucleus accumbens increases the expression of aggression in previously defeated hamsters. Bar graph shows the total duration (mean $\pm$ SEM) in sec of submissive/defensive, aggressive, social and nonsocial behavior exhibited by defeated hamsters during conditioned defeat testing. Animals received infusions of vehicle or cis(z)flupenthixol 5 min prior to being tested with a non-aggressive intruder.

*Significantly different from vehicle control ($p < 0.05$); ‡ Significantly different from anatomical hit drug group.

Figure 4.

Cis(z)flupenthixol infusion into the nucleus accumbens has no effect on agonistic behavior in non-defeated hamsters. This figure demonstrates the total duration (mean $\pm$ SEM) in sec of submissive/defensive, aggressive, social and nonsocial behavior exhibited by non-defeated hamsters during a 5-minute test with a non-aggressive intruder. No significant differences were found between groups in any of the behavioral categories.