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Adolescent social defeat alters markers of adult dopaminergic function

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Abstract

Stressful experiences during adolescence can alter the trajectory of neural development and contribute to psychiatric disorders in adulthood. We previously demonstrated that adolescent male rats exposed to repeated social defeat stress show changes in mesocorticolimbic dopamine content both at baseline and in response to amphetamine when tested in adulthood. In the present study we examined whether markers of adult dopamine function are also compromised by adolescent experience of social defeat. Given that the dopamine transporter as well as dopamine D1 receptors act as regulators of psychostimulant action, are stress sensitive and undergo changes during adolescence, quantitative autoradiography was used to measure [^{3}H]-GBR12935 binding to the dopamine transporter and [^{3}H]-SCH23390 binding to dopamine D1 receptors, respectively. Our results indicate that social defeat during adolescence led to higher dopamine transporter binding in the infralimbic region of the medial prefrontal cortex and higher dopamine D1 receptor binding in the caudate putamen, while other brain regions analyzed were comparable to controls. Thus it appears that social defeat during adolescence causes specific changes to the adult DA system, which may contribute to behavioral alterations and increased drug seeking.

Keywords

adolescent stress; dopamine, social defeat; dopamine transporter; dopamine D1 receptor

1. Introduction

Adolescence marks a period of critical change in which the mesocorticolimbic dopamine (DA) system undergoes substantial reorganization, enabling emotional and cognitive development that aids in the transition to adulthood [61, 70]. While such changes are inherently adaptive to survival, they also make the adolescent brain particularly vulnerable to insults from the experience of stressors [2, 3, 61]. Stress is a potent activator of the mesocorticolimbic DA system [1, 6], and evidence suggests that stressful experiences during

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adolescence can lead to long-term changes in this system that may contribute to increased incidence of psychiatric disorders in adulthood [7, 14, 23, 39, 47, 49, 62, 72, 74].

One particularly common yet severe stressor that adolescents encounter is bullying [45]. Along with its immediate consequences to psychological well-being, bullying is associated with a greater incidence of psychiatric disorders that may emerge either in adolescence or in later life [8, 25, 27, 36, 45, 65, 71]. In order to gain insight into the potential neural mechanisms by which bullying might contribute to later psychopathology, we have developed a rodent model of adolescent social defeat that mimics the victimization and imbalance of power defining human adolescent bullying [11, 72]. In line with the aforementioned developmental vulnerability of the mesocorticolimbic DA system, rats undergoing repeated social defeat in adolescence exhibit reduced dopamine content in the medial prefrontal cortex (mPFC) as adults [72]. Furthermore, amphetamine-induced increases in DA responses are attenuated in the mPFC of adult rats that had experienced adolescent social defeat [14]. Conversely, previously defeated rats showed an enhanced increase in amphetamine-induced DA responses in the nucleus accumbens (NAc) core compared to controls [14]. This particular pattern of low mPFC DA activity and high NAc DA activity has been associated with enhanced locomotion responses to both novelty and amphetamine, as well as increased psychostimulant self-administration [13, 51, 57, 67]. Indeed, rats exposed to social defeat in adolescence do show greater locomotion activity in novel environments as adults [14, 72], along with enhanced conditioned place preference for amphetamine [15]. Together, these findings suggest that the experience of social defeat in adolescence may have long term consequences on mesocorticolimbic DA regulatory processes that contribute to altered novelty and psychostimulant responses.

One point of DA regulation is the DA transporter (DAT), which acts as both a mechanism to clear synaptic DA and as a pharmacological target for amphetamine [55, 77]. Differences in DAT function and expression have also been found in rats with high versus low locomotion responses to novelty [28, 76]. Given findings of altered psychostimulant and novelty responses in previously defeated rats [14, 72], and that DAT levels are also affected by social defeat stress [22, 30, 40], we hypothesized that adolescent social defeat may lead to long-term changes in DAT expression. Besides DAT, the DA D1 receptor plays a role in facilitating amphetamine-induced locomotion behavior [26, 29, 68, 69, 75] and also participates in modulating the balance between mPFC and NAc DA levels [21, 48, 68, 69]. As rats defeated in adolescence also show decreased amphetamine-induced locomotion in adulthood compared to non-defeated controls [14], it was additionally hypothesized that DA D1 receptors may be altered by adolescent defeat experience. In order to investigate potential changes to these dopaminergic markers, we sought to analyze DAT and DA D1 receptors in mPFC, NAc, and striatum, as DA activity is affected by social defeat in these regions [30, 40, 66]. In addition, these structures are principally involved in mediating novelty and amphetamine-evoked responses on both a pharmacological and behavioral level [19, 51, 67, 77]. Thus, the present study utilized quantitative autoradiography to measure the binding of [^{3}H]-GBR12935 to DAT sites and of [^{3}H]-SCH23390 to DA D1 receptors in the mPFC, NAc, and striatum of adult rats that had undergone repeated social defeat in adolescence.

2. Materials and Methods

2.1. Subjects

Male juvenile post-weanling Sprague-Dawley rats (Postnatal day [P]21, n=20) were obtained from the University of South Dakota Laboratory Animal Services. All rats were pair-housed such that cage-mates were in the same treatment group (social defeat or control) and kept at 22 °C on a reverse 12-hr light-dark cycle (lights off 10.00). Food and water were

available *ad libitum.* Behavioral experiments were conducted between 11.00 and 15.00 under red lighting. All procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and received approval from the Institutional Animal Care and Use Committee of the University of South Dakota. Every effort was made to minimize the number of animals used and their suffering.

2.2. Social defeat

The adolescent social defeat procedure used in this study is a modification of the resident-intruder paradigm [34, 42, 43] and has been described in detail previously [14, 72]. Briefly, male rats (n=10), starting at P35 (mid-adolescence, [2, 61]), were introduced to the home cage of a larger aggressive resident adult male Sprague Dawley rat once daily for 5 consecutive days. After the adolescent intruder exhibited 3 consecutive submissive postures, it was considered defeated, and promptly confined behind a wire-mesh barrier within the resident's cage for 35 minutes. The adolescent rat was then subsequently returned to its home cage. Age-matched controls (n=10) did not experience social defeat, but were instead placed into a novel empty cage for the duration of the defeat trial in order to control for handling and novel environment stress. After the final defeat trial, all animals were allowed to mature undisturbed in their home cages until early adulthood (P56).

2.3. Brain Section Preparation

At P56, all subjects underwent rapid decapitation and brains were collected and frozen at −80 °C until use. Brain sections (16μm) were cut at −18°C in a cryostat microtome and mounted on gelatin-coated microscope slides (two brain sections per slide). Before storing at −80°C, all slides were kept overnight at 4°C under vacuum. For autoradiographic analysis, quadruplicate brain sections from each animal were used encompassing the mPFC (infralimbic, prelimbic and cingulate cortices) and corresponding to Plate 8 as listed in the brain atlas of Paxinos and Watson [50]. Similarly, quadruplicate sections from each subject that contained the nucleus accumbens (core and shell) and striatal caudate putamen (CPu) equivalent to Plate 12 of the Paxinos and Watson atlas [50] were also analyzed.

2.4. DAT binding

DAT binding was assessed with the radioligand [^{3}H]-GBR12935 according to the method described previously by Jiao et al. [31] with minor modifications. Slides containing sections were preincubated for 15 minutes at 4°C in a 7.5 pH buffer solution containing 50 mM NaH2PO4, 70 mMNaCl, 0.025% bovine serum albumin (BSA), 0.001% ascorbate, and 1 μMcis-flupentixol. This was followed by a 23 hour incubation in the same buffer solution with the addition of 2nM [^{3}H]-GBR12935. Non-specific binding was determined with the addition of 50μM mazindol. In order to the end the incubation, slides were placed in ice-cold buffer solution without [^{3}H]-GBR12935 for 2 hours. Slides were then dried at 4°C, transferred into cassettes and exposed to BioMax MS film with [^{3}H] standards. The exposure times were 14 days and 35 days for plates 12 and 8, respectively.

2.5. DA D1 receptor binding

DA D1 receptors were labeled with [^{3}H]-SCH23390 based on the method of Savasta et al. [56] and similar to that described previously [46]. Specifically, sections were preincubated for 15 minutes in a 7.4 pH buffer solution containing 50mM Tris-HCl, 120mM NaCl, 5mM KCl, and 1mM $MgCl_2$ at room temperature. The sections were then incubated for 60 minutes at room temperature in a similar buffer solution with the addition of 3.5nM [^{3}H]-SCH23390 and 30nM ketanserin tartrate (to block 5-HT_2 receptors). Non-specific binding was determined with the addition of 1μM (+)− butaclamol. The incubation was ended by dipping the slides in ice-cold buffer, followed by two consecutive 10 minute washes in ice-

cold buffer and a final dip in cold de-ionized water. The sections were then dried at room temperature and transferred into cassettes and exposed to Kodak BioMax MS film with [^{3}H] standards. The exposure times were 14 and 28 days for Plates 12 and 8, respectively.

2.6. Quantification and Statistics

Autoradiographic films were analyzed using the computer software program, ImageJ [54]. Nonspecific binding was subtracted from the total binding to provide the specific binding to either DAT or DA D1 receptors in the regions of interest.

Statistical analysis was performed using SigmaStat 3.5 for Windows. Data were expressed as mean ± S.E.M specific binding (fmol/mg brain protein), where protein levels are based on a standard curve of optical densities generated from a series of tritiated standards of known concentrations [31, 46]. Levels of DAT and DA D1 receptor binding in each region of interest were compared between previously defeated and control rats using separate one way ANOVA. The level of significance was set *a priori* at $p<0.05$.

3. Results

3.1. DAT binding to [^{3}H]-GBR12935

In the mPFC, significant increases in DAT binding density were found in the infralimbic cortex of adult rats that had undergone social defeat during adolescence ($F(1,17)=4.685$, $p=0.045$; Figure 1). However, previously defeated rats and controls showed equivalent levels of DAT binding in the prelimbic cortex ($F(1,17)=2.527$, $p=0.130$) and the cingulate cortex ($F(1,17)=4.373$, $p=0.052$) (Figure 1). No significant differences in DAT binding were found in the subcortical regions of the CPu ($F(1,17)=1.670$, $p=0.213$), NAc Shell ($F(1,17)=2.020$, $p=0.173$), or NAc Core ($F(1,17)=0.590$, $p=0.453$) (Figure 2).

3.2. DA D1 binding to [^{3}H]-SCH23390

In contrast to DAT binding density, no significant differences in DA D1 receptor binding between previously defeated rats and controls were found in the subregions of the mPFC (infralimbic ($F(1,18)=0.0891$, $p=0.769$); prelimbic ($F(1,18)=0.379$, $p=0.546$); cingulate $F(1,18)=0.947$, $p=.343$) (Figure 3). Likewise, DA D1 receptor binding did not differ between defeated and control rats in either the NAc core ($F(1,17)=0.939$, $p=0.346$) or the NAc shell ($F(1,17)=1.527$, $p=0.233$). However, previously defeated rats demonstrated increased DA D1 receptor binding density in the CPu ($F(1,17)=7.634$, $p=0.013$) as adults (Figure 4).

4. Discussion

4.1. Adolescent Social Defeat induces Changes in Adult DAT Binding

Rats that had experienced repeated social defeat in adolescence showed increased DAT binding in the infralimbic mPFC as adults. Given that a blunted mPFC DA response to acute amphetamine was previously observed in adult rats exposed to adolescent defeat [14], findings of the current study suggest that DAT availability is not a limiting factor for amphetamine action in the mPFC in these animals. Rather, this dampened DA response exhibited by previously defeated rats is most likely a function of reduced basal mPFC DA content caused by adolescent defeat [72].

Both physical and social stressors cause excessive mPFC DA release [1, 18, 66] in adult rats. Similarly, preliminary data using our model indicate that adolescent rats undergoing repeated defeat exhibit acute increases in mPFC DA release upon subsequent exposure to social threat [73], and it is also known that stress experienced during adolescence induces

greater mPFC neuronal activity than in adulthood [41]. Combined, this suggests that increased DAT density in the mPFC may reflect a compensatory mechanism to enhance clearance of excessive mPFC DA release caused by the stressful adolescent defeat experience, as has been observed in adult rats exposed to physical stressors [60]. While this would theoretically serve to help maintain efficient DA regulation in the face of repeated social defeat, its persistence beyond the stressful period into young adulthood could potentially contribute to the mPFC DA hypofunction and related behaviors of defeated rats we have described previously [14, 72]. In addition, heightened mPFC DA clearance resulting from increased DAT activity could directly enhance end-product inhibition of tyrosine hydroxylase to reduce DA synthesis [9], explaining why rats defeated in adolescence show decreased mPFC DA content as adults [72]. Evidence suggests the norepinephrine transporter (NET) plays an important role in mPFC DA clearance, possibly as a result of the relatively sparse distribution of DAT in the mPFC compared to other regions [44, 52]. Therefore, future studies should investigate whether mPFC NET expression and function is also affected by adolescent defeat and if this contributes to alterations in mPFC DA and related behaviors.

Rats defeated in adolescence show heightened locomotion responses in novel environments as adults [14, 72]. Zhu et al. [76] found that mPFC DAT function and cell surface expression in the mPFC were lower in rats with a high locomotion response to an inescapable novel environment, while no differences in total mPFC DAT binding were observed. With regards to DAT binding, the discrepancy of our findings with those of Zhu et al. [76] may be related to the method and model used in the current work, as our study used quantitative autoradiography to measure DAT binding in discrete mPFC subregions rather than homogenate binding within the entire mPFC. Furthermore, social defeat stress during adolescence may produce differential effects on mPFC DAT as compared to DAT profiles associated with naturally-occurring predispositions for high or low novelty responses without prior adolescent stress.

To our knowledge, this is the first study to evaluate the long-term effects of a social stressor in adolescence on DAT binding density, and the first to demonstrate that this effect on DAT is specific to the mPFC. Previous studies have shown that exposure to social defeat in adulthood results in changes to DAT expression, but unlike the current findings, these appear to be restricted to subcortical components of the limbic DA system, with no reported alterations to cortical DAT. Further, the direction of DAT change appears to depend on the defeat paradigm used. For instance, chronic social stress in adulthood causes an upregulation of accumbal and striatal DAT binding in subordinate male rats [40], while VTA DAT mRNA levels are increased in adult male mice that repeatedly experience social defeat [22]. In contrast, adult male rats exposed to a single social defeat show decreased striatal DAT binding, with this effect only apparent after being housed in isolation for >24 hr immediately following defeat [30]. The prefrontal cortex DA system undergoes dynamic alterations during adolescence [10, 20, 41, 64], components of which are delayed compared to subcortical DA structures [4, 12, 17]. Of relevance to the current findings, Leussis et al. [38] found that social isolation stress during adolescence produced decreases in synaptic density in both the infralimbic and cingulate cortex. Given that adolescent social defeat produced changes in DAT within similar regions, the present work supports literature in both animals [37, 38] and humans [5] that the developing prefrontal cortex is particularly vulnerable during adolescence to social stress, and as such may be responsible for the differing patterns of DAT expression seen in the current study compared with those using adult social stress paradigms.

4.2. DA D1 receptor binding

Adult rats that had undergone repeated social defeat during adolescence exhibited increased DA D1 receptor binding in the CPu, with no changes in regions of the NAc or mPFC. The DA D1 receptor is particularly important for facilitating locomotion responses to psychostimulants [75]. Although the current study found that previously defeated rats demonstrated increased CPu DA D1 receptor binding, these rats exhibit attenuated locomotion responses to amphetamine [14]. This is likely due to the fact that while the CPu is involved in amphetamine-induced stereotypy, DA activity in the NAc plays a more fundamental role in amphetamine-induced locomotion activity [32, 33, 58].

In viewing the increased DA D1 receptor binding in defeated rats from a developmental perspective, it is interesting to note that DA D1 receptors in the CPu undergo extensive pruning between adolescence and young adulthood [4, 24, 63]. These studies have shown that DA D1 receptor binding density reaches a peak in the CPu at P40 with an approximate 35-40% reduction by P60 [4, 63]. It is thus tempting to speculate that repeated social defeat stress ending at P39 prevented the normal DA D1 receptor pruning in the CPu that would be evident by the time the receptors were assayed at P56. The failure of defeated rats to demonstrate this pruning phenomenon may be due to changes in the mPFC DA system. It has been found that 6-OHDA lesions of the mPFC can produce upregulation of DA D1 receptors in the striatum [53], suggesting that the previously observed deficits in mPFC DA content following social defeat [72] may influence subcortical receptor content.

Andersen et al. [4] have suggested that DA receptor pruning in the CPu may be related to decreases in hyperactivity symptoms seen in attention deficit hyperactivity disorder (ADHD) after periadolescence. Such reasoning is in line with observations that the spontaneously hypertensive rat (SHR), which is used as model for ADHD, has higher DA D1 receptor binding in the CPu compared to other strains [16, 35] (but see [59]). Given the hyperactive-like nature of previously defeated rats [14, 72], assessing DA receptor binding at multiple time points would provide more insight into how the experience of stressors during adolescence affect normal development of the DA system and might contribute to disorders such as ADHD.

4.3. Conclusions

When exposed to repeated social defeat in adolescence, male rats demonstrate regional alterations in DAT and DA D1 receptor binding density as adults. Specifically, previously defeated rats were found to have significant increases in DAT binding in the infralimbic region of the mPFC, while DA D1 receptor binding was significantly increased in the CPu. The persistence of these changes into adulthood is likely reminiscent of the developmental vulnerability of the adolescent brain to stress [2, 3, 61]. Given the role of DAT and DA D1 receptors in regulating DA, the alterations found in the present study may contribute to the long-term changes in behavior and psychostimulant responses seen previously in rats exposed to adolescent defeat [14, 72]. In order to further our understanding of the long-term consequences of severe adolescent stressors, future studies utilizing pharmacological challenges to target DAT and DA D1 receptors will better characterize the mechanisms by which changes in binding density found in the present study relate to alterations in brain function and behavior.

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Abbreviations

DA	Dopamine
DAT	Dopamine Transporter
mPFC	medial prefrontal cortex
NAc	nucleus accumbens
CPu	caudate putamen

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Novick et al – Research Highlights

- Stressful experiences in adolescence can disrupt neural development.
- We show adult prefrontal cortex dopamine transporter increases after adolescent social defeat.
- Previously defeated rats also showed increased striatal dopamine-1 receptors.
- These changes may underlie altered drug responses seen after adolescent defeat.

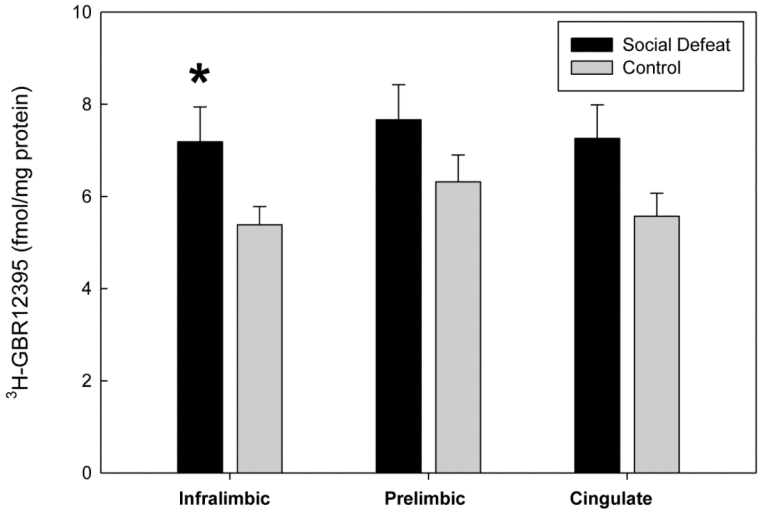

Figure 1.

Specific binding of [^{3}H]-GBR12935 to DAT sites in regions of the mPFC of adult rats that underwent adolescent social defeat versus controls. Data are expressed as the mean±S.E.M. of measurements from 10 rats from each group with determinations made in quadruplicate sections from each brain. * Significant difference between treatment groups ($p<0.05$).

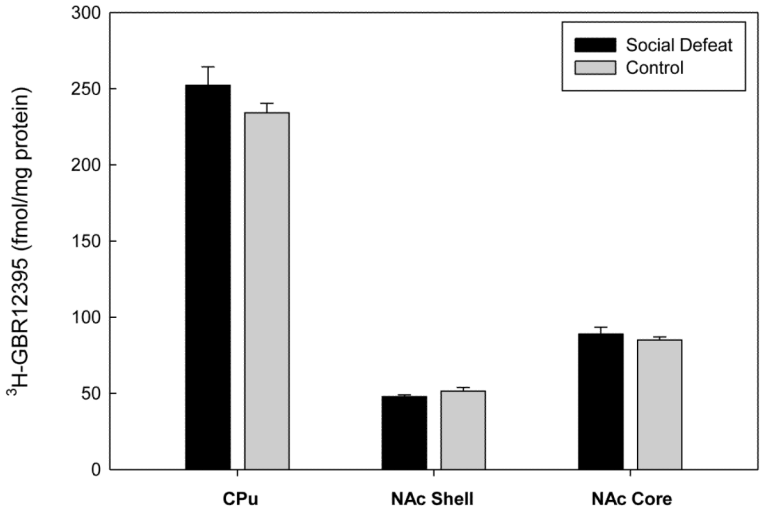

Figure 2.

Specific binding of [^{3}H]-GBR12935 to DAT sites in subcortical regions of adult rats that underwent adolescent social defeat versus controls. Data are expressed as the mean±S.E.M. of measurements from 10 rats from each group with determinations made in quadruplicate sections from each brain.

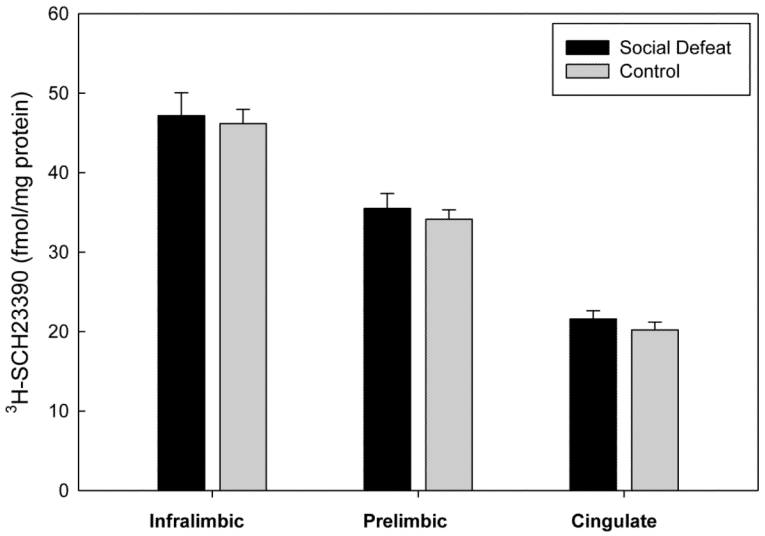

Figure 3.

Specific binding of [^{3}H]-SCH23390 to DA D1 receptor sites in regions of the mPFC of adult rats that underwent adolescent social defeat versus controls. Data are expressed as the mean ±S.E.M. of measurements from 10 rats from each group with determinations made in quadruplicate sections from each brain.

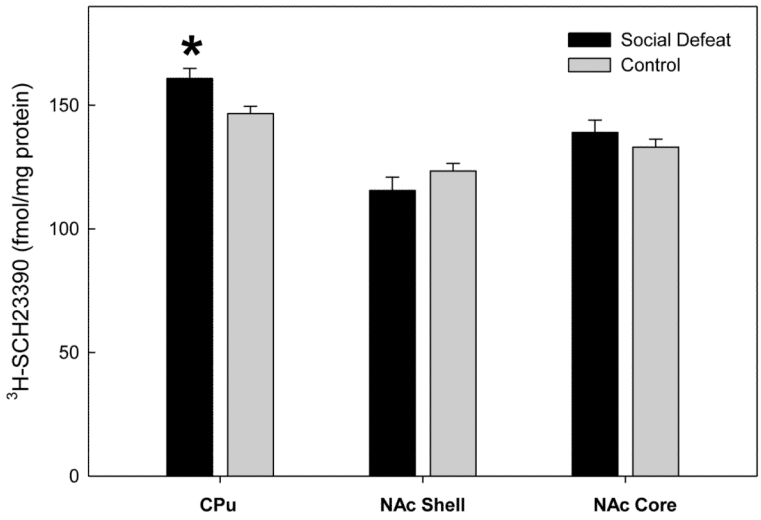

Figure 4.

Specific binding of [^{3}H]-SCH23390 to DA D1 receptor sites in subcortical regions of adult rats that underwent adolescent social defeat versus controls. Data are expressed as the mean ±S.E.M. of measurements from 10 rats from each group with determinations made in quadruplicate sections from each brain. * Significant difference between treatment groups ($p<0.05$).