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NICOTINE SENSITIZATION AND BRAIN-DERIVED NEUROTROPHIC
FACTOR CONTENT IN ADOLESCENT RATS NEONATALLY TREATED
WITH QUINPIROLE

Thesis submitted in partial fulfillment of Honors

By

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Abstract

Neonatal treatment of quinpirole in rats increases dopamine D2-like receptor sensitivity over the animal's lifetime, a phenomenon referred to as D2 priming. Male and female Sprague-Dawley rats were given quinpirole (1mg/kg, i.p.) or saline on postnatal days (P)1-21. After habituation to a locomotor arena on P29-31, beginning P33, animals were administered nicotine (0.3 mg/kg, 0.5 mg/kg, or 0.7 mg/kg, i.p.) or saline and placed into a locomotor arena for behavioral testing every second day for a total of 9 treatments. The results showed that adolescents neonatally treated with quinpirole produced more enhanced sensitization to nicotine than controls. Brains tissues were analyzed for brain-derived neurotrophic factor (BDNF), a protein involved in neuron development and maintenance. The results showed that neonatal quinpirole treatment produced a significant increase in accumbal BDNF. Also, adolescent nicotine treatment produced a significant increase in BDNF in the nucleus accumbens and dorsal striatum. These findings help to broaden understanding of behavioral and chemical changes involved in schizophrenia and nicotine use and could have applications in aiding to alleviate this common comorbidity.

Introduction

Nicotine abuse is common among many psychological disorders (Ziedonis et al., 2008). Notably, previous studies have shown that up to 70% of schizophrenic population smokes cigarettes (LeDuc & Mittleman, 1995). This is a smoking rate of 2-5 times that of the normal population (Lasser et al., 2000; Leon & Diaz, 2005). In addition, lower cessation rates have been noted in schizophrenic individuals (Leon & Diaz, 2005). This suggests that schizophrenic individuals have a more difficult time quitting smoking. Most tobacco use begins in adolescence, and it has been found to be more difficult to quit smoking during adolescence because biological differences exist that make this time period easier to become addicted to nicotine (Kota, Martin, & Damaj, 2008; Levin et al., 2007; US Department of Health and Human Services, 1994). Because chronic smoking is shown to have detrimental health effects and continues to be the leading cause of preventable morbidity and mortality (Centers for Disease Control and Prevention, 2004), much research has been done to understand the behavioral and chemical changes associated with nicotine use in a schizophrenia model.

Previous work in this laboratory has used a rodent model for schizophrenia through neonatal administration of quinpirole, a D2/D3 receptor agonist, to rats. This drug treatment has been shown to produce an increase in D2-like receptor sensitivity over the lifetime of the animal, also referred to as “D2 receptor priming” (Kostrzewa, 1995; Brown et al., 2005; Brown, Perna, Schaefer, & Williams, 2006; Thacker et al., 2006). Validation of this increase has been demonstrated through the analysis of the expression of Rgs (Regulator of G-protein) 9. Neonatal quinpirole treatment has been shown to produce decreases of Rgs9 in the nucleus accumbens, striatum, and frontal cortex (Maple et al., 2007). There have been similar findings of decreased

Rgs9 expression in postmortem studies in schizophrenic individuals (Seeman et al., 2007). Thus, this finding is an important validation of this model.

Brain derived neurotrophic factor (BDNF) is a neurotrophic factor involved in neuronal development and maintenance and synaptic connectivity. Previous work in this laboratory has shown that adult rats that were neonatally treated with quinpirole results in decreases in BDNF in the hippocampus and frontal cortex (Brown, Perna, Schaefer, & Williams, 2006; Thacker et al., 2006). This is consistent with the finding that postmortem brain samples from individuals with schizophrenia and mood disorders demonstrated significant reduction in BDNF expression in several regions of the brain (Ray, Weickert, Wyatt, & Webster, 2011). Correlated with lower truncated-BDNF levels in schizophrenic individuals is higher positive and lower negative PANSS scores and worse performance in cognitive assays (Carlino et al., 2011). One study with male rats has shown that nicotine results in an increase of BDNF levels in the hippocampus and cortex in adult rats (Czubak et al., 2009). Although, previous work in this laboratory with adult male and female rats has shown nicotine is related to decreases in BDNF in the hippocampus and frontal cortex (Brown, Perna, Schaefer, & Williams, 2006). Nicotine has also been shown to increase accumbal BDNF levels in adolescent rats (Correll et al., 2009). Furthermore, BDNF levels in schizophrenic individuals have been shown to be significantly higher in smokers as compared to nonsmokers and have also been shown to be correlated with fewer negative symptoms (Zhang et al., 2010). These results suggest that BDNF levels may have a relationship to the severity of symptoms in schizophrenic patients.

The current study aimed to broaden understanding of behavioral and neurochemical changes in the brain due to nicotine administration in adolescent D2-primed rats. Nicotine sensitization was analyzed in adolescent male and female rats neonatally treated with quinpirole.

It was hypothesized that D2-primed rats would express enhanced locomotor sensitization when administered nicotine due to increased sensitivity of dopamine D2-like receptors and based past results from this laboratory showing increased behavioral sensitization (Sheppard, Lehmann, Cope, & Brown, 2009). Also, BDNF was analyzed in brain tissue areas of the accumbens, dorsal striatum, and frontal cortex. It was hypothesized that, as compared to controls, accumbal BDNF levels would be higher in nicotine treated rats based on previous research showing similar increases (Correll et al., 2009). It was also hypothesized that, as compared to controls, BDNF levels would be abnormal in quinpirole treated rats.

Materials and Methods

Subjects

A total of 12 adult untimed pregnant female Sprague-Dawley rats were obtained from Harlan, Inc. (Indianapolis, IN), and their offspring, 59 males and 51 females, were used as subjects for this study. The day of birth was considered postnatal day 0 (P0). At P21, the subjects were weaned, and housed, socially, two to four animals per cage. Animals were housed in climate-controlled environment on 12-hr light-dark cycle with food and water available ad libitum. Neonates were randomly assigned to an ontogenic drug treatment, quinpirole or saline, and also randomly assigned to an adolescent drug treatment, nicotine or saline. To control for within-litter variance, only one male and one female from each litter were assigned to each of the drug treatments (Holson & Pearce, 1992). All procedures in this experiment were approved by the University Committee on Animal Care at East Tennessee State University.

Apparatus

A locomotor arena and Any Maze (Stoelting, Wood Dale, IL) tracking system were used in the adolescent nicotine sensitization procedure to record locomotor activity. This arena,

painted flat black, was square and measured 91.44 cm on a side and 30.48 cm deep. A camera was placed 228.6 cm above the arena and was connected to Any Maze tracking system recording locomotor activity.

Drug treatment procedure

Beginning on P1, animals were administered, i.p., quinpirole HCL (1mg/kg) or saline daily until P21. The rats were weaned at P21 and raised to P29. Beginning on P29, animals were habituated to a locomotor arena. For 3 consecutive days, (P29-P31), animals were injected, i.p., with saline, and then 10 minutes later, placed in the arena for 10 minutes. Beginning P33, nicotine sensitization testing began, and animals were tested every other day for a total of nine trials (P33-P49). During nicotine sensitization, animals were injected, i.p., with nicotine (0.3 mg/kg, 0.5 mg/kg, or 0.7 mg/kg) or saline, and then 10 minutes later, placed in the arena for 10 minutes of testing. On P50, a subset of animals' brain tissue was taken for BDNF analysis. The medial frontal cortex, nucleus accumbens, and dorsal striatum were dissected from the brain and stored at -80°C until assayed. The number of animals in the subset analyzed for BDNF in each group is described as follows with neonatal drug treatment denoted Q for quinpirole or S for saline, and adolescent drug treatment denoted N5 for nicotine (0.5mg/kg) and S for saline: QN5= 4, QS= 5, SN5= 3, SS= 5.

BDNF assay procedure

Tissues were prepared by homogenizing with mortar and pestle, sonicating, and centrifuging for 20 minutes at 14,000 G. Supernatant was then removed and samples were stored at -20°C overnight. Protocol was followed as defined by the supplier (Promega, Madison, WI, USA) for BDNF assay. In summary, the anti-BDNF monoclonal antibody (mAB) was diluted 1:1000 in carbonate coating buffer (pH 9.7), and 100 µL of this was added to every well of a

polystyrene ELISA plate (Nunc, MaziSorb) and overnight, incubated at 4°C. The wells were then emptied and washed with a TBST wash buffer. After washing, non-specific binding was blocked by adding 200 µL of a block and sample 1X buffer and deionized water mixture to every well. The plate was incubated at room temperature for 1 h. The plate was then washed, and the BDNF standard curve was prepared using the BDNF standard supplied by the manufacturer which was diluted 1:2000 with block and sample 1X buffer. In the first two columns on the first row, 200 µL of the diluted standard were added. Six 1:2 serial dilutions were performed in each of the first two columns. Sample dilutions were also prepared and added in duplicate to wells. The plate was incubated with shaking for 2h at room temperature. After washing the plate, Anti-Human BDNF polyclonal antibody (pAb), diluted 1:5000 in block and sample 1X buffer, was added to each well (100 µL) and incubated with shaking at room temperature for 2 h. The plate was then washed, and an Anti-IgY horseradish peroxidase conjugate, diluted 1:2000 in block and sample 1X buffer, was added to each well (100 µL) and incubated with shaking at room temperature for 1 h. After washing the plate, 100 µL of tetramethyl benzidine (TMB) one solution was added to each well and incubated with shaking at room temperature for 10 minutes. The reaction was stopped by adding 100 µL of 1 N hydrochloric acid, and the plate was read within 30 minutes at 450nm absorbance.

Research design

For statistical analysis of nicotine sensitization testing, a 2 x 2 x 2 x 4 ANOVA was utilized. For analysis, there were four factors in this design including sex (male, female), neonatal drug treatment (quinpirole, saline), day of testing (Day 1, Day 9), and adolescent drug treatment (nicotine 0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg, saline). These two days of testing were chosen for statistical analysis because it represents acute and chronic nicotine treatment. For

statistical analysis of BDNF, a 2 x 2 two-way ANOVA was used. For this analysis, there were two factors in this design including neonatal drug treatment (quinpirole, saline) and adolescent drug treatment (nicotine 0.5mg/kg, saline). Sex was not included as a factor in BDNF analysis because of the low number of subjects in the subset analyzed.

Results

Nicotine sensitization

Initial analysis

A 2 x 2 x 2 x 4 ANOVA showed significant main effects of neonatal drug treatment, $F(1,92) = 46.53, p < .001$, adolescent drug treatment, $F(1,92) = 55.14, p < .001$, and day of treatment $F(1,92) = 76.05, p < .001$. Also, significant interactions were shown with sex vs. adolescent drug treatment, $F(3,92) = 2.86, p < .041$, neonatal drug treatment vs. adolescent drug treatment, $F(1,92) = 9.82, p < .001$, and adolescent drug treatment vs. day, $F(3,92) = 15.53, p < .001$. A three-way significant interaction was also shown with neonatal drug treatment x adolescent drug treatment x day, $F(3,92) = 3.25, p < .025$. Also, quinpirole treated neonates given the highest nicotine dosage showed significant increase in activity at days 1 and 9 of treatment as compared to all other groups.

Acute dosing analysis

Figure 1a (females) and 1b (males) present horizontal locomotor activity as a function of drug treatment. A 2 x 2 x 4 ANOVA on day 1 behavioral performance during nicotine treatment showed significant main effects of neonatal drug treatment, $F(1,109) = 11.99, p < .001$ and adolescent drug treatment, $F(3,109) = 38.28, p < .001$. Also, significant interaction, $F(3,109) = 6.22, p < .001$, of neonatal drug treatment vs. adolescent drug treatment was shown. Post hoc

analyses revealed that quinpirole treated neonates given the highest dosage of nicotine had significantly higher levels of activity than all other groups.

Chronic dosing analysis

Figure 2a (females) and 2b (male) present horizontal locomotor activity as a function of drug treatment. A 2 x 2 x 4 ANOVA showed significant main effects of neonatal drug treatment, $F(1,107) = 34.71, p < .001$, adolescent drug treatment, $F(3,107) = 31.80, p < .001$. Also, significant interactions were found of sex x adolescent drug treatment, $F(3,107) = 5.05, p < .003$, and neonatal drug treatment x adolescent drug treatment, $F(3,107) = 6.78, p < .001$. Similar to the above analysis in acute adolescent drug treatment, quinpirole treated neonates given the highest nicotine dosage had higher levels of activity as compared to all other groups, but this response was more robust in males than females.

Brain-derived neurotrophic factor

Figures 3a (nucleus accumbens), 3b (dorsal striatum), and 3c (frontal cortex) show the amount of BDNF protein (pg/mg) as a function of drug treatment in each brain area. In the nucleus accumbens, a 2 x 2 ANOVA showed a significant main effect of neonatal drug treatment, $F(1, 18)=4.723, p<0.049$, and adolescent drug treatment, $F(1, 18)=4.925, p<0.045$. Treatment of quinpirole neonatally produced significant increases in accumbal BDNF, and adolescent treatment of nicotine also produced significant increases in accumbal BDNF. In the dorsal striatum, a 2 x 2 ANOVA showed a significant main effect of adolescent drug treatment, $F(1, 18)=11.376, p<0.005$. Nicotine treatment in adolescence produced a significant increase in BDNF in the dorsal striatum. In the frontal cortex, a 2 x 2 ANOVA showed a significant interaction of neonatal drug treatment and adulthood drug treatment, $F(1,18)=5.296, p<0.039$. This showed neonatal saline rats treated with nicotine had higher BDNF levels than any other

group. There were no significant interactions in the nucleus accumbens or dorsal striatum and no significant main effects in the frontal cortex.

Discussion

The present study revealed several important findings on nicotine sensitization and BDNF content in adolescent rats. First, it was shown that rats neonatally treated with quinpirole will express enhanced locomotor sensitization during chronic nicotine treatment as compared to controls, and this effect was more robust in males than females. Furthermore, neonatal quinpirole treatment produced enhanced sensitization to nicotine drug treatment except in the highest nicotine dosage. When given the highest nicotine dosage at the acute treatment, neonatal quinpirole treatment enhanced the locomotor response without enhancing sensitization. The study also revealed that adolescent nicotine treatment produced significant increases in BDNF in the nucleus accumbens and dorsal striatum. Also, neonatal quinpirole treatment to adolescent rats produced an increase in BDNF protein in the nucleus accumbens. Nicotine administration to adolescents neonatally treated with saline also showed enhanced levels of BDNF in the frontal cortex.

The finding that adolescent rats neonatally treated with quinpirole enhanced sensitization to nicotine is consistent with previous results from this laboratory (Sheppard, Lehmann, Cope, & Brown, 2009). Further, adolescent males neonatally treated with quinpirole also demonstrated a more robust behavioral response to nicotine as compared to females. Because locomotor sensitization to nicotine has been shown to be intricately related to the dopaminergic system, the results of this study suggest that increasing sensitivity of D2-like sensitized the dopaminergic response to nicotine (Vezina, McGehee, & Green, 2007). This also suggests that nicotine

produces an enhanced positive reinforcing behavioral response which may explain higher rates of smoking and lower cessation rates in schizophrenic populations (Leon & Diaz, 2005).

The increase in BDNF in the striatum after nicotine treatment found in this study was consistent with previous work which has shown that treatment of nicotine in rats produces significant increases in striatal BDNF mRNA levels (Maggio et al., 1998). Also, the finding that BDNF in the nucleus accumbens increases due to nicotine treatment in adolescent rats treated is consistent with previous findings in this laboratory using mice as subjects (Correll et al., 2009). An increase in BDNF was also found in the frontal cortex of saline treated neonates that were administered nicotine in adolescence which is also consistent with previous findings (Czubak et al, 2009). An increase in BDNF was found in the nucleus accumbens of adolescent rats neonatally treated with quinpirole. This finding is different from other studies that show neonatal quinpirole treatment produces decreases BDNF levels in various regions of the brain, but this study used adolescent rats; whereas, previous studies have used adult rats (Brown, Perna, Schaefer, & Williams, 2006; Thacker et al., 2006). This shows that changes in the BDNF response to neonatal quinpirole are possibly dependent on age in a developing adolescent brain. One limitation of BDNF analysis in this study includes low sample size. The increase in BDNF found in this study could be an important finding relative to a relationship to addictive behavior in which has also been revealed in work with the psychostimulant amphetamine (Meredith, Callen, & Scheuer, 2002). This increase in BDNF could affect neuronal development in adolescence and lead to changes in dopaminergic responses. BDNF has been shown to increase dopamine release and has long been shown to be important in the survival of dopaminergic neurons, and thus, the current results suggest that changes in the levels of BDNF could have

significant effects on dopaminergic neurons, especially in a developing adolescent brain (Blöchl & Sirrenberg, 1996; Hyman et al., 1991).

In conclusion, animals given neonatal quinpirole treatment appear to demonstrate an increased sensitivity to nicotine. Increased levels of BDNF in the nucleus accumbens and dorsal striatum region of the brain due to nicotine treatment also show that nicotine appear to be involved in changes in neuronal development and maintenance. This shows that nicotine use in psychosis could have serious effects on brain development in adolescence. The current study could have implications towards studies aiming to alleviate the difficulty of quitting nicotine use in adolescence psychosis.

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Figures

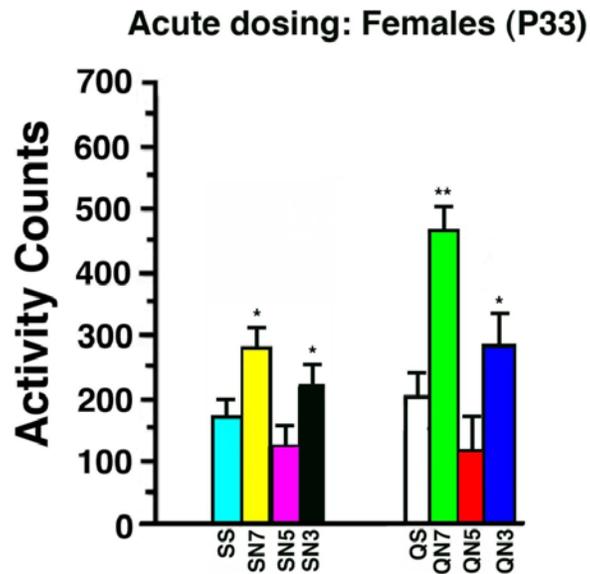


Figure 1a: Acute nicotine dosing in adolescent female rats. Group QN7 demonstrated higher levels of activity than all other groups. Also, Groups QN3, SN3 and SN7 showed higher levels of activity compared to controls.

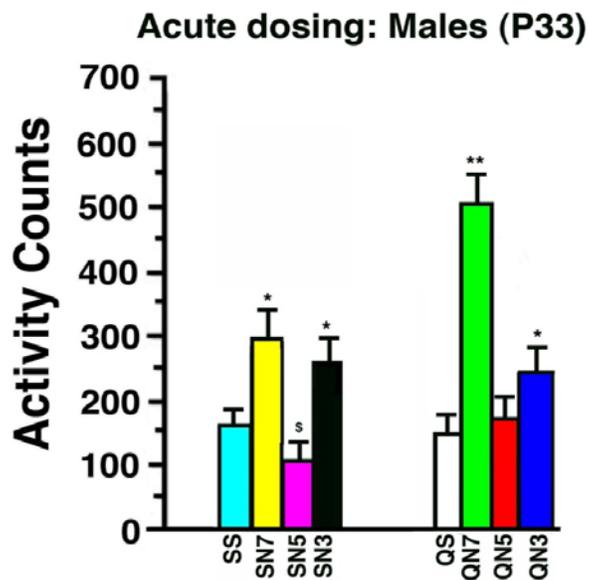


Figure 1b: Acute nicotine dosing in adolescent male rats. Group QN7 demonstrated higher levels of activity than all other groups. Also, Groups QN3, SN3 and SN7 showed higher levels of activity compared to controls. Group SN5 showed lower levels of activity compared to controls.

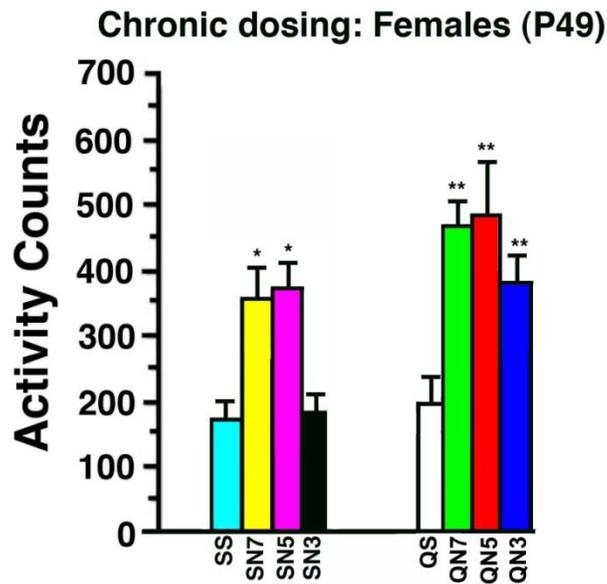


Figure 2a: Chronic nicotine dosing in adolescent female rats. Groups QN3, QN5, and QN7 showed enhanced nicotine sensitization compared to controls. Groups SN5 and SN7 showed sensitization relative to Group SS.

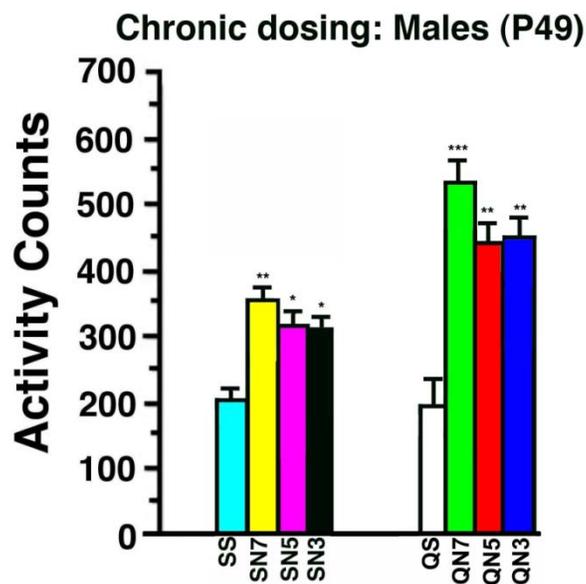


Figure 2b: Acute nicotine dosing in adolescent male rats. Group QN7 demonstrated higher levels of activity than all other groups. Also, Groups QN3 and Group QN5 showed higher levels of activity compared to Groups SN3 and Group SN5.

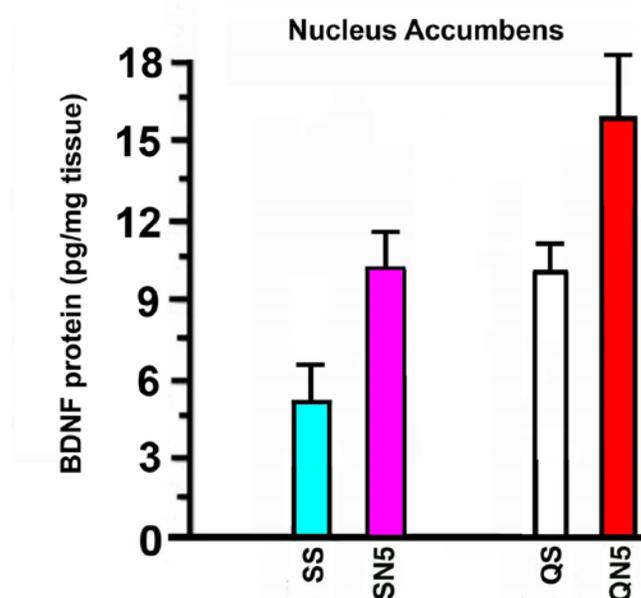


Figure 3a: BDNF protein concentration (pg/mg tissue) for nucleus accumbens. There was significant increase shown in Group SN5 and Group QN5 as compared to Group SS and Group QS and Group QN5 as compared to Group SS and SN5.

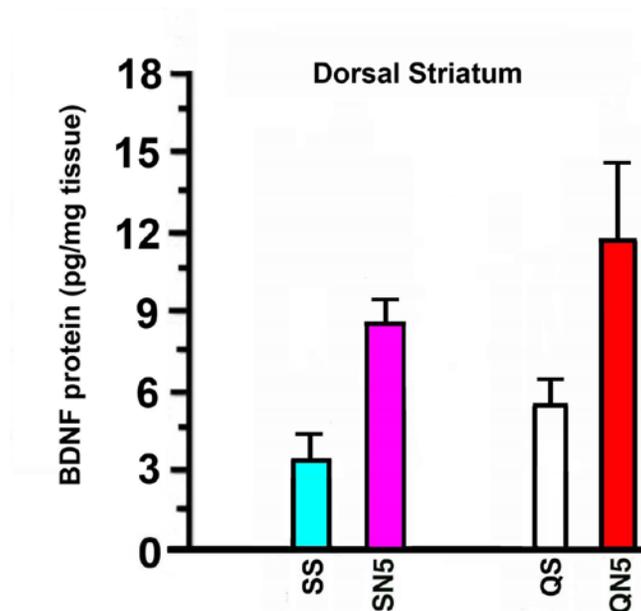


Figure 3b: BDNF protein concentration (pg/mg tissue) for dorsal striatum. There was significant increase shown in Group SN5 and Group QN5 as compared to Group SS and Group QS.

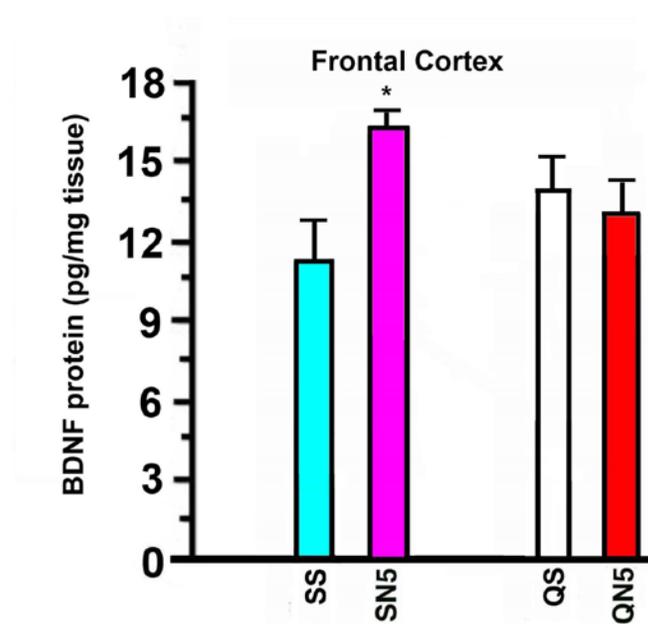


Figure 3c: BDNF protein concentration (pg/mg tissue) for frontal cortex. There was a significant increase shown in Group SN5 as compared to all other groups.