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Altered dopaminergic profiles: implications for the regulation of voluntary physical activity

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Abstract

The biological regulating factors of physical activity in animals are not well understood. This study investigated differences in central mRNA expression of seven dopamine genes (*Drd1*, *Drd2*, *Drd3*, *Drd4*, *Drd5*, *TH*, and *DAT*) between high active C57/LJ (n=17) male mice and low active C3H/HeJ (n=20) male mice, and between mice with access to a running wheel and without running wheel access within strain. Mice were housed with running wheels interfaced with a computer for 21 days with distance and duration recorded every 24 hours. On day 21, the striatum and nucleus accumbens were removed during the active period (~9pm) for dopaminergic analysis. On average, the C57L/J mice with wheels ran significantly farther (10.25±1.37 km/day vs. 0.01±0.09 km/day, p<0.001), longer (329.73±30.52 mins/day vs. 7.81±6.32 mins/day, p<0.001), and faster (31.27±3.13 m/min vs. 11.81±1.08 m/min, p<0.001) than the C3H/HeJ mice with wheels over the 21 day period. No differences in gene expression were found between mice in either strain with wheels and those without wheels suggesting that access to running wheels did not alter dopaminergic expression. In contrast, relative expression for two dopamine genes was significantly lower in the C57L/J mice compared to the C3H/HeJ mice. These results indicate that decreased dopaminergic functioning is correlated with increased activity levels in C57L/J mice and suggests that D1-like receptors as well as Tyrosine Hydroxylase (an indicator of dopamine production), but not D2-like receptors may be associated with the regulation of physical activity in inbred mice.

Keywords

dopamine; locomotion; running wheel; mice; dopamine receptor; striatum; nucleus accumbens

Introduction

It is axiomatic that physical activity is important to human health. Given the known benefits of physical activity, it is imperative to understand the mechanisms that regulate this behavior. It has been well established in both human and animal models that genetic factors significantly influence physical activity levels (12,20,24,25,27,29,30,47,50). However, the identity of which systems or genes are involved in the regulation of activity level is currently unclear.

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The central function of the dopaminergic system is to control motivation for natural rewards and motor movement (52), and several studies in rodents suggest certain aspects of dopaminergic functioning may contribute to the genetic/biological regulation of physical activity (5,37,39,46). There are five known dopamine receptors classified into two different sub-types based on genetics and function. D1 and D5 receptors are classified as “D1-like receptors”, while D2, D3, and D4 receptors are classified as “D2-like receptors”. Differing aspects of the dopamine system, such as specific receptor subtypes, have been implicated in movement disorders such as Attention Deficit Hyperactivity Disorder (36), and Parkinson's Disease (23). Furthermore, the midbrain dopamine system has been shown to mediate reward and reinforcement for several behavioral functions. For example Salamone and colleagues (43) have rightfully reported that the dopamine system is intricately involved in both motor control and reward, and the complexity of this regulation allows for modulation of complex motor processes. It has long been thought that the dopamine system played a role in the reward and/or reinforcement of behavioral functions (45), and it is now suggested that the dopamine system plays a major role in specifically the “wanting” of a natural reward such as food, as opposed to the “liking” of the natural reward (44). For example, El-Ghundi et al (11) state: “dopamine D1 receptor plays a role in the motivation to work for reward (palatable food) but not in reward perception.” Thus, given the suggestion that nucleus accumbens dopamine may be an interface between motivation and action (33), this neurotransmitter system is a likely candidate to regulate voluntary physical activity.

Several studies have linked aspects of the dopamine system to various facets of locomotion in animals (2,3,5,8,16,22,32,46). However, the term “locomotion” in animal literature broadly refers to the act of movement, which can encompass a wide variety of specific definitions depending on the methodology used (e.g. spontaneous locomotion, open field locomotion). Voluntary physical activity (in particular on a wheel in the home cage), which could be described as a very specific type of locomotion, is commonly defined as purposeful exercise or movement that expends a significant amount of energy. Thus voluntary physical activity may be a separate phenotype, from other general locomotion or movement phenotypes, because there is purpose and motivation involved. Although many types of locomotion found in the literature are considered “voluntary”, and directly relate to the study of the role of the dopamine system in voluntary movement, no studies have been conducted to investigate the role of the dopaminergic system in the regulation of *voluntary* physical activity on wheels in inbred strains of mice. Artificial selection studies in mice have shown that mice bred for high wheel running respond differently than controls to drugs such as Cocaine or Ritalin which act by blocking the dopamine transporter (39). In addition, Rhodes and colleagues found that D1-like antagonists reduced wheel running more in control line mice compared to selected animals, while D2-like antagonists had similar effects on both selected and control mice, suggesting D1-like receptors may be important in mediating the increased wheel running in the selected animals (38). Fink and Reis (13) showed that BALB/cJ mice have more dopamine cell bodies, and tyrosine hydroxylase activity in both the nigrostriatal, and mesolimbic pathways in the brain compared to CBA/J. Similarly the researchers point out that Balb/cJ mice and CBA/J mice also differ in behavioral responses to drugs which act by means of affecting dopamine release in the midbrain, and suggest that genetic differences in midbrain dopamine signaling between inbred strains may account for behavioral differences in response to certain psychoactive substances (13). Taking this a step further, it is also possible that genetic differences in the dopamine system in mice may translate into intrinsic (or natural) behavioral differences, such as certain aspects of locomotion, or motivation for physical activity.

Whilst dopaminergic functioning may act as an independent variable to regulate physical activity, it has also been shown that changes in the dopamine system such as increased dopamine activity and/or neural synthesis can be dependent upon physical activity (42,48,51, 53). From the current studies available (5,13,38-40,46) it is unclear if dopamine functioning

is acting independently on physical activity levels or if physical activity is affecting dopaminergic functioning. Therefore, this study investigated whether the dopamine system acts as the dependent or independent variable in the regulation of physical activity by assessing expression differences in seven dopamine related genes in the striatum/nucleus accumbens area of the brain.

Methods

Animals

C57L/J mice, previously shown to be high active animals and C3H/HeJ mice, previously shown to be low active animals were used in this study (29). Mice were purchased from The Jackson Laboratory (Bar Harbor, ME). Both strains have been inbred past 130 generations, and exhibit no phenotypic abnormalities that would confound this study. Only male mice were used in this study to avoid possible confounding effects of the menstrual cycle on daily physical activity in female mice (1). All mice were housed in the University Vivarium with 12 hour light/dark cycles and were provided food (Harlan Teklad 8604 Rodent Diet, Madison, WI) and water *ad libitum*. All procedures were approved by the University of North Carolina Charlotte Institutional Animal Care and Use Committee.

In order to investigate whether the dopamine system is acting in a dependent or independent fashion in the regulation of physical activity, mice from each strain were randomly assigned to experimental groups housed with running wheels (C57L/J, n=10; C3H/HeJ, n=10), or control groups housed with no running wheels (C57L/J, n=7; C3H/HeJ, n=10). Only 7 control C57L/J mice were used because of difficulty in supply availability from The Jackson Laboratory. Each group was housed and treated the same other than the presence of a wheel in the experimental group. At 8 weeks of age experimental group mice were housed with a wheel to allow for one week of acclimation. All mice were approximately 9 weeks of age at the beginning of data collection for the study.

Measurement of Voluntary Daily Activity Level

Daily wheel running in mice was chosen as the model of human voluntary physical activity level (10) and was measured using methods described previously (29,30). Briefly, mice were housed individually with a running wheel (450mm circumference; Ware Manufacturing, Phoenix, AZ) mounted in each cage. The wheels were equipped with a magnet mounted on the outside surface and the top of the cage was equipped with a magnetic sensor (BC500; Sigma Sport, Olney, IL). Each cage computer was calibrated (per manufacturer's instructions) for the circumference of the cage wheel allowing for accurate measurement of distance (km) and time the animals ran on the wheel (duration in min). The data were collected every 24 hours for 21 days and the wheels were checked manually each day to assure sensor alignment and free-turning. Speed of activity (m/min) was calculated by dividing daily distance by daily duration of exercise. Additionally, weight of all animals was recorded weekly.

Molecular Analysis

Brains were harvested whole and the striatum and nucleus accumbens area was dissected out over ice and immediately flash frozen in liquid nitrogen and stored at -80°C. The nucleus accumbens and striatum were identified after the brain was cross-sectioned to separate the two hemispheres, the hippocampus was identified and removed from view, and the striatum and nucleus accumbens appeared as an "orange slice" textured area on the interface of the right and left cortex regions. Tissues were harvested between 9 pm and 12 am, corresponding to hours 4 through 6 of the active cycle (12 hour light/dark cycle with the dark cycle between 6pm and 6am) in order to capture dopaminergic activity during the active period.

Quantitative real time RT-PCR was conducted using standard protocols to analyze mRNA expression of the following dopaminergic genes: dopamine receptor 1 (*Drd1*), dopamine 2 receptor (*Drd2*), dopamine 3 receptor (*Drd3*), dopamine 4 receptor (*Drd4*), dopamine 5 receptor (*Drd5*), tyrosine hydroxylase (*TH*), and the dopamine transporter (*Slc6a3* also known as *DAT*). Primers were designed using Primer 3 (Steve Rozen and Helen J. Skaletsky) (41) and ordered from Integrated DNA Technologies Inc (San Diego, CA). Total mRNA from the striatum and nucleus accumbens samples were isolated using trizol reagent (Sigma-Aldrich, Saint Louis, MO), and cDNA was prepared using QuantiTect Rev. Transcription Kit (QIAGEN, Valencia, CA). Real time analysis was conducted using QuantiTect SYBR Green PCR Kit (QIAGEN, Valencia, CA) and the LightCycler@1.5 Carousel-Based System (Roche Applied Science, Indianapolis, IN). All dopamine receptor mRNA expressions were normalized to an endogenous positive control (beta-actin) using methods as described previously (35).

Statistics

Two-way ANOVA (JMP 7.0, SAS Institute, Cary, NC) was used to compare expression of all seven genes for the main effects of strain (C57L/J high active or C3H/HeJ low active) and group (wheel-running or non-wheel running). The alpha value was set at 0.05 and Tukey's HSD *post-hoc* tests were used to evaluate significant main effects were present to evaluate strain by group interactions.

Results

Voluntary Physical Activity

As expected from past research, the C57L/J mice were significantly more active than the C3H/HeJ mice (Figure 1). C57L/J mice with wheel access ran significantly farther (10.25 ± 1.37 km/day vs. 0.01 ± 0.09 km/day, $p < 0.001$), longer (329.73 ± 30.52 mins/day vs. 7.81 ± 6.32 mins/day, $p < 0.001$), and faster (31.27 ± 3.13 m/min vs. 11.81 ± 1.08 m/min, $p < 0.001$) than C3H/HeJ mice with wheel access during 21 days of wheel running data collection. There was no difference ($p = 0.67$) in starting weights between C57L/J mice (25.6 ± 1.0 g) and C3H/HeJ mice (25.6 ± 1.1 g). There were also no significant differences ($p > 0.05$) in weight within C3H/HeJ mice between group or over time [Control group: beginning weight = 25.8 ± 0.9 g, end weight = 26.1 ± 1.5 g; Running wheel group: beginning weight = 25.8 ± 1.2 g, end weight = 27.0 ± 1.4 g]. Additionally, within the C57L/J mice, no significant changes in weight were seen over time within group ($p > 0.05$); [Control group: beginning weight = 26.1 ± 1.5 g, end weight = 26.8 ± 1.3 g; Running group: beginning weight = 25.3 ± 0.7 g, end weight = 26.5 ± 0.9 g].

mRNA Expression

No significant differences in expression of any of the genes were found between wheel-running and non-wheel-running groups within each strain (Figure 2 and Figure 3). However, significant differences were found between strains in the expression of the dopamine genes. The expression of *Drd1* ($p < 0.0001$, power = 0.90), and *TH* ($p = 0.0008$, power = 0.90) (Figure 4) were markedly different between the high active and low active mice. C57L/J mice (high active) expressed significantly lower amounts of mRNA of each of these genes in the striatum/nucleus accumbens than did the C3H/HeJ mice (Figure 4). Expression of *Drd5* ($p = 0.05$; power = .44) bordered on significance between strains; however, this marginal difference in *Drd5* is not surprising considering that *Drd1* and *Drd5* are in the same sub-family of dopamine receptors. No differences in gene expression between strains were found for *Drd2* ($p = 0.01$; power = 0.4), *Drd3* ($p = 0.21$; power = 0.2), *Drd4* ($p = 0.27$; power = 0.2), and *DAT* ($p = 0.83$; power = 0.05).

Discussion

The genetic and biological regulating factors of physical activity are only beginning to be understood. This study showed that genetically different strains of mice not only differ in their physical activity levels, but that these differences are perhaps mediated at least in part by the dopamine system. Specifically, it was shown that C57L/J male mice run significantly farther, longer, and faster than C3H/HeJ male mice (Figure 1). No differences in expression of any of the dopamine receptors, as well as *TH*, and *DAT* genes were found as a result of access to a running wheel thus suggesting that activity was not altering gene expression level of dopamine receptors or enzymes in the midbrain. Finally, significant differences were found between the high and low active animals for both *Drd1* and *TH* dopaminergic genes. Both *Drd1* and *TH* were expressed at significantly lower levels in C57L/J (high active) mice compared to the C3H/HeJ (low active) mice. In conjunction with past literature relating dopaminergic functioning with activity, our results further support the hypothesis that the dopaminergic system independently regulates physical activity possibly through the *Drd1* receptors and tyrosine hydroxylase.

The results of this study highlight an important first step in the understanding of the genetic/biological regulation of physical activity. Voluntary physical activity has been shown to have a significant genetic component underlying the manifestation of this trait. Heritability studies estimate the genetic contribution to physical activity ranges from 20-80% (12,24,27,29,34, 50). Recent studies by Lightfoot and colleagues have also begun to elucidate possible quantitative trait loci (QTL) associated with regulation of physical activity in mice including a QTL that contains the *Drd1* gene (30). Although not the only genetic or biological influence on physical activity, the current study highlights the possible importance of differences of overall expression of various dopaminergic genes (in particular *Drd1* and *TH*) in the mid-brain in mediating differences in physical activity levels between genetically different inbred strains of mice.

Many studies have been conducted investigating possible peripheral differences (e.g. mitochondrial number, muscle fiber type) between strains or groups of mice which may account for differing wheel running activity levels. However, the few peripheral differences that have been studied do not account for the wide variation in wheel running observed in different strains of mice indicating a central component may also be important in regulating this type of behavior. Several studies conducted using mice bred for high wheel running activity indicate a possible “central” regulation of wheel running behavior (9,14,15,17,18). Specifically, mice bred for high wheel running have altered regional brain activation profiles compared to control mice (39), as well as respond differently to dopaminergic acting drugs (38,40). Similarly, pharmacological studies have shown that depletion of dopamine from the mid-brain induces hypolocomotion (26), while stimulant administration generally induces hyperlocomotion (21). Thus, in this paper we hypothesized the dopamine system is an important central genetic factor involved in the regulation of physical activity behavior in inbred strains of mice. Similarly, the nucleus accumbens/striatum were investigated in this study because this area of the midbrain has been implicated in motor movement as well as motivation and reward behaviors (43).

It is well known that the dopamine system is important in mediating certain aspects of locomotion in animals. In addition to the dopamine system's known role in the motor movement disabilities manifested in Parkinson's disease (19), dopaminergic functioning has also been implicated in the hyperactive phenotype typical of Attention Deficit Hyperactivity Disorder (ADHD). The results of the current study suggest that high wheel running mice have decreased expression of *TH*, and decreased expression of D1 receptors in the midbrain. Whether or not this decreased expression of D1 receptors and TH corresponds to altered downstream signaling

is yet to be determined and is only speculative. Although our research is not directly related to ADHD phenotypes, there is speculative evidence that certain behavioral phenotypes in ADHD appear to be a result of lower dopamine presence in the synapse and thus altered overall dopamine signaling (28,31). When given cocaine or GBR 12909, both DAT inhibitors, mice selectively bred for high amounts of wheel running decreased their wheel running more than controls (40). We did not find a difference in the expression of DAT in the current study; however, this differential finding may be due to differences between the mechanistic underpinnings of high activity versus ADHD, and direct comparisons are probably not possible. Nevertheless, it is intriguing that the high active mice in this study had significantly lower amounts of *TH* in the striatum/nucleus accumbens area compared to low active mice indicating the amount of dopamine production and turnover is lower in high active inbred mice, and may be important for overall physical activity levels.

It is important to point out that the finding of decreased dopaminergic function in high active mice is contradictory to pharmacological data showing that dopamine depletion in the nucleus accumbens generally causes decreased locomotion in mice (26), while stimulant drugs acting by increasing the amount of extracellular dopamine generally increase locomotion in mice (49). These differential findings suggest one of two possibilities: 1. When analyzed from a purely genetic perspective, dopaminergic regulation of motivation for wheel running may indeed be different than the regulation suggested in other types of locomotion studies, or 2. The use of different techniques (pharmacological, vs. genetic) to assess the role of the dopamine system in regulation of physical activity may yield different results due to unknown confounding factors. Never-the-less, this highlights the importance of understanding the motivational factors involved in regulating such a complex behavioral phenotype.

Some studies using selectively bred mice for high wheel running do correspond with our findings in the current study. Rhodes and Garland investigated the effects of several dopaminergic acting drugs on wheel running in mice bred for high amounts of wheel running and compared their responses to control line mice. They found that apomorphine (a non-selective dopamine agonist) and SCH 23390 (a selective D1-like antagonist) decreased wheel running more in the control lines compared to the selected lines, while treatment with raclopride (a selective D2-like antagonist) had similar effects on wheel running in both the selected and control lines (38). The authors suggested these results indicated the selected animals had a decreased function of the D1-like receptors, but not the D2-like receptors, and these differences may mediate motivational differences for high voluntary amounts of running in the selected animals. Our results correspond with the results from Rhodes and Garland, in that a decreased function of the D1-like receptors in a high active inbred strain compared to a low active inbred strain of mice was apparent, and suggests these receptors are important in the regulation of physical activity behavior, possibly in the form of motivation for this voluntary behavior.

It has been unclear whether the dopamine system acts as a dependent or independent factor in the regulation of physical activity. It has been shown that exercise causes changes in neurotransmitter systems, including an increase in dopamine production, and these responses lead to beneficial changes at the molecular and cellular levels including increased neuronal plasticity, cognitive functioning, learning, and overall mood (7). The neurotransmitter alterations are a primary reason that exercise is often used in the treatment of depressive disorders (4). While activity may influence dopaminergic functioning, previous work, especially that from Garland's group as well as the known role of the dopamine system in regulation of motivation and reward (6,44), led us to hypothesize that genetically, the dopamine system may also play an important independent role in the regulation of physical activity. Said another way, genetic differences in the dopamine system between inbred mice may directly mediate differences in physical activity on a running wheel, instead of the activity itself acting to alter the dopamine system. Our findings of similarities in brain dopaminergic gene

expression within strain, regardless of whether the mice were exposed to a running wheel, suggests that expression levels of these genes are not necessarily subject to fluctuation based on wheel activity levels. The differences we observed between strains in *Drd1* and *TH* suggest that these particular genes may be acting to mediate the large differences seen in activity levels between these two strains of mice.

The evidence presented in this study is an important first step to understanding the multifaceted genetic and biological regulation of voluntary physical activity levels. As mentioned previously, the genetic contribution to regulation of physical activity ranges from 20-80%; however, we are only beginning to understand the genetic regulating factors of this behavioral trait. The present study suggests the dopamine system may be an important central genetic factor involved in regulation of physical activity. In addition, this study is the first to show that lower expression of the D1 receptor, as well as tyrosine hydroxylase in the mid-brain, may possibly mediate the high activity seen in the C57L/J strain. The authors acknowledge the limitation of only investigating two strains, however these strains were specifically chosen based on wheel running strain screens of approximately 35 different strains because they exhibited drastically different wheel running activity behavior. Further investigation of the genetic influence of the dopamine system on physical activity should include more strains with mid-range activity level. Also, given that the dopamine system itself is influenced by factors such as nutritional status, and hormones and that the dopamine system also regulates several downstream signaling pathways leading to differential gene expression, the central, genetic regulation of voluntary physical activity is an intriguing avenue of study and certainly bears significance in the prevention of inactivity related diseases.

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Figure 1. Average distance, duration, and speed for C57L/J (n=10) and C3H/HeJ (n=10) mice over 21 days. **A.** Average distance (Km/day) for C57L/J (10.25±1.37) and C3H/HeJ (0.01±0.09). **B.** Average duration (mins/day) for C57L/J (329.73±30.52) and C3H/HeJ (7.81±6.32) mice. **C.** Average speed (m/min) for C57L/J (31.27±3.13) and C3H/HeJ (11.81±1.08) mice. Standard deviations are reported * designates significantly higher than C3H/HeJ mice at $p < 0.001$.

Figure 2.

Gene expression in the striatum/nucleus accumbens tissue of C3H/HeJ mice housed with a running wheel and C3H/HeJ mice housed without a running wheel. No expression differences ($p > 0.05$) were found between control ($n=10$) and running ($n=10$) C3H/HeJ mice for any of the seven dopaminergic genes. Standard deviations are reported.

Figure 3.

Gene expression in the striatum/nucleus accumbens tissue of C57L/J mice housed with a running wheel and C57L/J mice housed without a running wheel. No expression differences ($p > 0.05$) were found between control ($n=7$) and running ($n=10$) C57L/J mice for any of the seven dopaminergic genes. Standard deviations are reported.

Figure 4.

A significant main effect of strain was found for two dopaminergic genes (*Drd1*, and *Tyrosine Hydroxylase*). For each of these genes, C57L/J mice had significantly lower expression than C3H/HeJ mice. Standard deviations are reported. p values are reported for each gene in the figure. * indicates significance at $p < 0.05$.