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Striatal enkephalinergic differences in rats selectively bred for intrinsic running capacity

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ABSTRACT

Rats selectively bred for high- and low-capacity for running on a treadmill (HCR; LCR) also differ in wheel-running behavior, but whether wheel-running can be explained by intrinsic or adaptive brain mechanisms is not as yet understood. It is established that motivation of locomotory behavior is driven by dopaminergic transmission in mesolimbic and mesostriatal systems. However, whether voluntary wheel running is associated with enkephalinergic activity in the ventral striatum is not known.

Materials and methods: 40 male (20 HCR and 20 LCR) and 40 female (20 HCR and 20 LCR) rats were randomly assigned to 3 weeks of activity wheel exposure or sedentary conditions without wheel access. After 3 weeks of activity-wheel running, rats were decapitated and brains were extracted. Coronal sections were analyzed utilizing in situ hybridization histochemistry for enkephalin (ENK) mRNA in the ventral striatum.

Results: HCR rats expressed less ENK than LCR rats in the nucleus accumbens among females ($p<0.01$) and in the olfactory tubercle among both females ($p<0.05$) and males ($p<0.05$). There was no effect of wheel running on ENK mRNA expression.

Conclusion: Line differences in ENK expression in the olfactory tubercle, and possibly the nucleus accumbens, partly explain divergent wheel-running behavior. The lower striatal ENK in the HCR line is consistent with enhanced dopaminergic tone, which may explain the increased motivation for wheel running observed in the HCR line.

1. Introduction

Family and twin studies indicate that variation in human physical activity levels is heritable (Eriksson et al., 2006; Simonen et al., 2002; Stubbe et al., 2006), but the genetic determinants of physical activity are poorly understood (Dishman, 2008). Voluntary wheel running by rodents also has a genetic component (Knab and Lightfoot, 2010;

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Lightfoot et al., 2004,2008; Roberts et al., 2013; Swallow et al., 1998; Waters et al., 2013). Rats selectively bred at the University of Michigan for high-capacity running (HCR) or low-capacity running (LCR) (Koch and Britton, 2001) demonstrate substantial divergence in treadmill performance, including running speed and distance (Høydal et al., 2007; Koch and Britton, 2008) and also daily wheel-running (Groves-Chapman et al., 2011; Waters et al., 2008), an activity that appears to represent a preferred and evolutionarily salient behavior in rodents (Belke and Wagner, 2005; Brené et al., 2007; Iversen, 1993; Lett et al., 2000; Sherwin, 1998).

The HCR line is associated with several traits subordinate to exercise performance, including a greater capacity to deliver and utilize O_2 in skeletal muscle (Howlett et al., 2009; Gonzalez et al., 2006), but these differences do not fully account for the large differences in running behavior between lines. Instead, these variations may reflect traits that mediate the relationship between a central drive to engage in motor behavior and observed locomotion (Jónás et al., 2010; Novak et al., 2010). The HCR and LCR rats provide a model from which the brain pathways underlying heritable running behavior and gene-environment interaction can be investigated (Koch and Britton, 2008).

Although the neurobiology of motivated wheel running is as yet unknown, there is substantial evidence for a mechanism involving the mesolimbic–motor interface (Burgess, 2010; Knab et al., 2009; Scheurink et al., 2010).The cumulative evidence suggests this junction exists at the basal ganglia (Garcia-Rill, 1986; Mogenson, 1987; Parent and Hazrati, 1995; Smith et al., 1988; Takakusaki et al., 2004), particularly in striatal GABA/opioidergic neurons located in distinct areas of the striatum that receive dopaminergic projections from the ventral tegmental area (Cardinal et al., 2002; Depue and Collins, 1999; Horvitz, 2002).

Striatal GABAergic medium spiny neurons express D2-like dopamine receptors and enkephalin or D1-like receptors and dynorphin in the direct (striatonigral) pathway and indirect (striatopallidal) pathway, respectively (Gerfen and Young, 1988; Surmeier et al., 1996). Midbrain dopaminergic transmission sensitizes the striatum to rewarding stimuli, mediates the incentive salience associated with these stimuli (Berridge and Robinson, 1998; Ikemoto, 2007; Morales-Mulia et al., 2013), increases in response to acute (Hattori et al., 1994) and chronic treadmill training (Gilliam et al., 1984), and is up-regulated in the striatum of mice selectively bred for high levels of activity-wheel running (Mathes et al., 2010). The motivational drive to run is plausibly mediated by striatal enkephalinergic neurotransmission in the nucleus accumbens septi (NAS) and olfactory tubercle (OT) or through the efferent targets of these neurons in the ventral pallidum (Le Moine et al., 1990; Young et al., 1986). The striatal enkephalin-dopamine environment may be important for understanding voluntary locomotory behavior (Dishman and Holmes, 2012; Kalivas et al., 1983). Enkephalin (ENK) is a peptide neuromodulator of GABAergic projections to the ventral pallidum (the limbic structure contiguous with motor pathways) that appears to suppress motor activity and motivated behavior (Durieux et al., 2009; Ena et al., 2011; Kravitz et al., 2010). Wheel-running behavior in rats may be directly attributable to differences in ENK expression (Werme et al., 2002), and divergent running performance observed between HCR and LCR rats may be explained by differences in striatal ENK expression. We hypothesized that HCR rats would have less ventral striatal ENK expression than LCR rats and that three weeks of access to wheel-running would down-regulate ENK expression in the ventral striatum compared to a sedentary housing condition.

2. Results

2.1. *Running distance and body weight*

Weekly running was reliable across the three weeks in females, intraclass correlation (ICC) (2,3)=0.875 and in males, ICC (2,3)=0.900. Running increased over time in females, $F(2,36)=14.486$, $\varepsilon=0.846$, $\eta^2=.45$, $p<0.001$, and males, $F(2,36)=4.45$, $\varepsilon=.980$, $\eta^2=0.20$, $p<0.05$. There was an effect of line in females, $F(1, 18)=47.289$, $\eta^2=0.72$, $p<0.001$, and in males, $F(1, 18)=13.766$, $\eta^2=0.43$, $p<0.01$. HCR rats ran more on average than LCR rats, but there was also a line × quadratic trend across time in females, $F(1,18)=10.192$, $\eta^2=0.36$, $p=0.005$. There was a quadratic effect of time independent of line in males, $F(1,18)=4.927$, $\eta^2=0.22$, $p=0.04$. Among females, weekly running distance increased linearly in LCR, $F(1,9)=12.212$, $\varepsilon=0.564$, $\eta^2=.58$, $p=0.007$, but it reached a plateau after week 2 in HCR, $F(1,9)=8.168$, $\varepsilon=0.908$, $\eta^2=0.48$, $p=0.017$. Among males, running distance increased linearly in LCR, $F(1,9)=$(Fig. 1).

Body weight was reliable across the five weeks in females, ICC (2,3)=0.978, and in males, ICC (2,3)=0.986. Body weight increased linearly over time in females, $F(2,72)=653.246$, $\varepsilon=1.0$, $\eta^2=0.95$, $p<0.001$, and in males, $F(2,72)=954.299$, $\varepsilon=1.0$, $\eta^2=.964$, $p<0.001$. There was an effect of line in

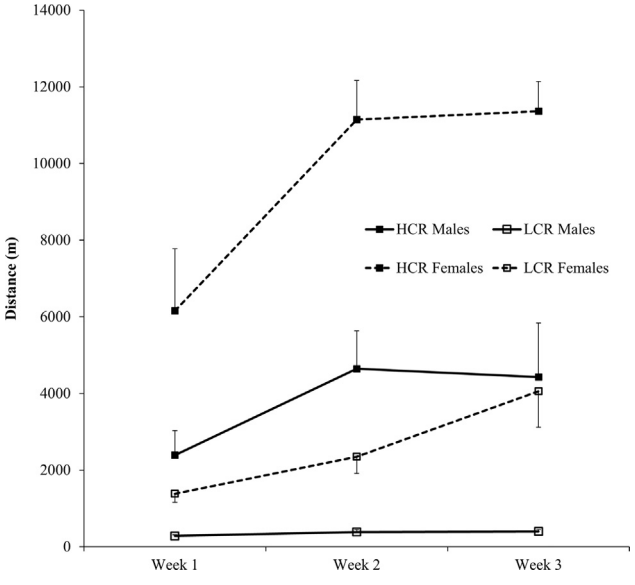

Fig. 1 – Mean daily running distances (± SEM) on the activity-wheel over 3 weeks. High-capacity running (HCR) rats ran more on average than low-capacity running (LCR) rats. There was an interaction effect between lines over 3 weeks in females; the effect was independent of line in males.