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Addiction-Prone Lewis But Not Fischer Rats Develop Compulsive Running that Coincides with Downregulation of Nerve Growth Factor Inducible-B and Neuron-Derived Orphan Receptor 1

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We have examined the effects of chronic voluntary running for 30 d on the levels of nerve growth factor inducilble-B (NGFI-B) and neuron-derived orphan receptor 1 (NOR1) mRNAs in Fischer and Lewis rats. The aim was to compare the addiction-prone Lewis rat strain to the Fischer strain in a plausible model for natural reward. The Lewis strain ran markedly more than the Fischer strain, as indicated by the length of running per day when given free access to running wheels. Both strains progressively increased their amount of daily running. By day 14, Lewis rats had reached a maximal level corresponding to 10 km/d, which slowly decreased to ~8 km/d. Fischer rats ran considerably less, averaging ~1.5 km/d by day 30. After 30 d of running, levels of mRNA encoding NGFI-B and Nor1 were decreased in cerebral cortex in Lewis but not Fischer rats. The downregulation of NGFI-B mRNA in Lewis rats could not be attenuated by the opioid receptor antagonist naloxone. Instead, naloxone by itself downregulated NGFI-B in striatum and cerebral cortex in both strains. In contrast, naloxone had no effect on Nor1 mRNA levels, although the running-induced downregulation of Nor1 was, in most cases, attenuated by naloxone. Data from the present study suggest that the same genetic factors contributing to the drug addiction-prone behavior of Lewis rats also control the excessive running behavior and that this coincides with downregulation of transcription factors of the NGFI-B family.

Key words: abuse; basal ganglia; in situ *hybridization; exercise; stress; withdrawal; NR4A1; NR4A2; NR4A3*

Animal models comparing inbred rat strains are often used in studies characterizing genetic factors in addiction and stress (George and Goldberg, 1989; Nestler, 1992). The Lewis rat has a higher preference to self-administer or to develop place preference for cocaine, morphine, ethanol, and nicotine compared with the Fischer rat (Suzuki et al., 1988a,b; Kosten et al., 1994; Horan et al., 1997). Fischer and Lewis rats are inbred from the Sprague Dawley rat, and drug-naive Lewis rats display many features in the mesolimbic dopamine pathway that are similar to those of addicted or chronically stressed Sprague Dawley rats (Nestler, 1992). Fischer rats have higher basal levels of corticosterone than Lewis rats (Dhabhar et al., 1993; Ortiz et al., 1995). In addition, stress leads to higher sustained levels of corticosterone in Fischer than in Lewis rats (Dhabhar et al., 1993; Ortiz et al., 1995; Gomez et al., 1996). Overall, the Fischer rat is more sensitive to stress then the Lewis rat.

Nerve growth factor inducible-B (NGFI-B), neuron-derived ophan receptor 1 (NOR1), and nur(77)-related 1 (Nurr1) belong to a family of nuclear orphan receptors with unknown ligands (Mangelsdorf et al., 1995). They are expressed within the mesolimbic and mesostriatal dopamine system, which is functionally involved in drug addiction, Parkinson's disease, and schizophrenia. NGFI-B and Nor1 are expressed under basal conditions in accumbens and striatum (Zetterström et al., 1996a,b), whereas Nurr1 is expressed in dopaminergic neurons and also has a role in dopamine neurogenesis (Zetterström et al., 1997). NGFI-B is induced in hypothalamus after chronic and acute stress (Chan et al., 1993; Rivest and Rivier, 1994). NGFI-B and glucocorticoids have opposite actions on the regulation of the pro-opiomelanocortin gene in the pituitary (Drouin et al., 1998). NGFI-B mRNA levels are also activated by ethanol (Ogilvie et al., 1998), caffeine (Svenningsson et al., 1995), ischemia (Lin et al., 1996), and dopamine D2 receptor agonists (Svenningsson and Fredholm, 1997).

Physical activity is assumed to maintain and enhance physical and mental health. Long-term regular exercise in human subjects is reported to increase self-esteem and relieve anxiety (Bahrke, 1979; Greist et al., 1979; Sonstroem and Morgan, 1989). In spontaneously hypertensive rats, CSF β-endorphin levels are increased by voluntary chronic running and remain high for the first 2 d after interruption of running, after which they decrease (Hoffmann et al., 1990b). This decrease coincides with increased aggressive behavior, and is thus possibly caused by cessation of chronic running and the consequent endorphin withdrawal (Hoffmann et al., 1987, 1990b).

Our aim was to investigate whether inbred rat strains that differ in response to addictive drugs and stress also differ in running behavior. We show that the drug-preferring Lewis rat strain also has a higher preference for excessive running. In addition, we demonstrate that compulsive chronic running downregulates mRNA encoding the transcription factors NGFI-B and Nor1. Our findings implicate a role for NGFI-B and Nor1 in neural circuits associated with addiction and stress.

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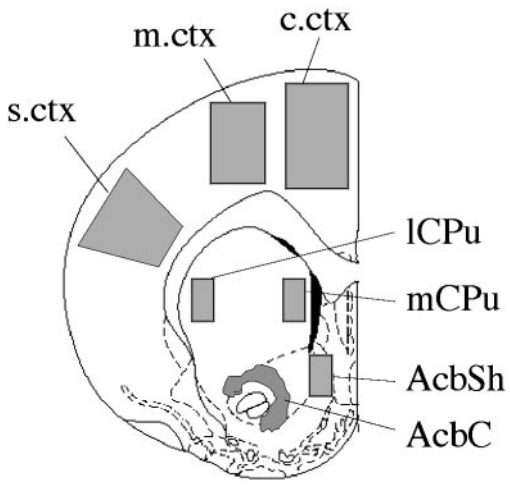

Figure 1. Quantitative computerized image analysis was performed over the indicated *shaded areas*. Analysis was performed at approximately the level of bregma 1.60 mm [figure modified from plate 12 in Paxinos and Watson (1997)]. *lCPu*, Lateral caudate putamen; *mCPu*, medial caudate putamen; *AcbSh*, accumbens shell; *AcbC*, accumbens core; *c.ctx*, cingulate cortex; *m.ctx*, motor cortex; *s.ctx*, sensory cortex.

MATERIALS AND METHODS

Male Fischer 344 and Lewis 250 gm rats (Møllegaard Breeding Center, Skensved, Denmark) with access to food and water *ad libitum* were housed in individual cages. Those animals having access to running wheels (diameter, 34 cm; one revolution corresponding to 1.07 m) had unlimited access. The running behavior of each animal was recorded using a computer-based data collection system. Naloxone (2 mg/kg, s.c.) was administered 2 hr before dissection of the animals. Because most running behavior occurred during nighttime and because rats were dissected between 12:00 P.M. and 1:30 P.M., they were not dissected at the time of active running.

In situ *hybridization.* Animals were killed, and brains were frozen on dry ice. The protocol for *in situ* hybridization was according to Dagerlind et al. (1992). Coronal brain sections (14 μm) were cut on a cryostat at −20°C. The sections were thawed onto glass slides. The hybridization cocktail contained 50% formamide, 4× SSC (1× SSC is 0.15 M NaCl and 0.015 sodium citrate, pH 7.0), 1× Denhardt's solution, 1% Sarcosyl, 0.02 M Na_3PO_4, pH 7.0, 10% dextran sulphate, 0.06 M DTT, and 0.1 mg/ml sheared salmon sperm DNA. For detection of NGFI-B, (1191–1238) (Milbrandt, 1988), Nurr1 (1430–1477) (Law et al., 1992), and Nor1 (1191–1238) (Ohkura et al., 1994) mRNAs, 48-mer oligonucleotides complementary to described nucleotides were used. The oligonucleotide probes were 3′-end labeled with α-^{35}S-dATP (DuPont NEN, Wilmington, DE) using terminal deoxynucleotidyl transferase (Life Technologies, Gaithersburg, MD) to a specific activity of $\sim 1 \times 10^9$ cpm/mg. The labeled probe was then separated from unincorporated nucleotides (Nensorb-20 column; DuPont NEN), and 5×10^6 cpm of probe was added per milliliter of hybridization cocktail. Each section was incubated with 0.1 ml of the hybridization cocktail. Hybridization was performed for 18 hr in a humidified chamber at 42°C. After hybridization, sections were rinsed four times for 20 min each in 1× SSC at 60°C. Finally, sections were rinsed in autoclaved water for 10 sec, dehydrated in alcohol, and air dried. Thereafter, the slides were exposed to film (Hyperfilm; Amersham, Arlington Heights, IL) for 1–3 weeks.

Image analysis. Optical density values from *in situ* hybridizations were quantified on a computerized image analysis system (NIH Image analysis program, version 1.62). Measurements were performed in the *shaded areas* covering the indicated brain regions in Figure 1. To correlate optical density values on the autoradiograms to amount of radioactivity (nanoCuries per gram) corresponding to ^{35}S-labeled mRNAs, a ^{14}C step standard (Amersham) was used.

Statistical procedures. Data were analyzed using a two-way ANOVA (Statistica, version 4.1 for Macintosh; StatSoft, Inc., Tulsa, OK) with repeated measurements in seven different areas to examine strain and treatment differences.

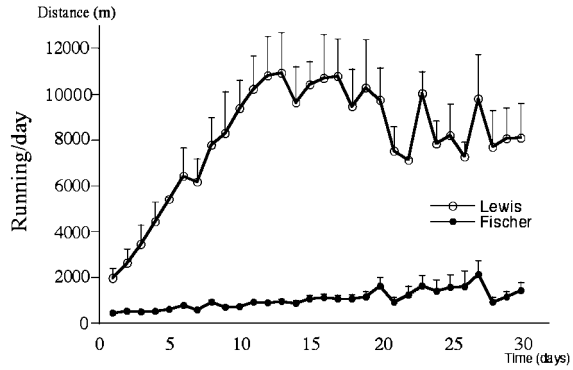

Figure 2. Running behavior in running wheels. Lewis and Fischer rats were individually housed and had free access to running wheels for 30 d. Activity in the wheels is converted to meters. The rats were mostly active during nights. Values are means ± SEM (n = 8).

RESULTS

Running behavior

During the first 24 hr that naive Lewis rats used running wheels, distances corresponding to ~2000 m were achieved (Fig. 2). They increased their daily running until day 13–14 when they averaged ~10,000 m/d (Fig. 2). Running behavior stabilized at a high level from approximately day 13 until day 21. There was consequently a trend of decreasing daily running distance until day 30 when the experiment ended. Naive Fischer rats ran only ~400 m during the first 24 hr (Fig. 2). They then gradually increased their daily running, and by the last day of the experiment (day 30), they ran ~1500 m.

Naloxone treatment

To analyze whether the high levels of endogenous opioids noted in chronic running (Hoffmann et al., 1990b) could cause physical dependence, the opioid receptor antagonist naloxone (2 mg/kg, s.c.) was administered to possibly precipitate physical withdrawal symptoms similar to those after chronic morphine administration. However, no increased signs of seizures, diarrhea, rearing, or loss of body weight were detected (data not shown). Therefore, we cannot conclude from our experiments that the rats developed physical dependence based on the increased production of endogenous opioids.

Basal levels of NGFI-B, Nor1, and Nurr1 mRNA in rats housed individually for 3 weeks without access to running wheel

Similar basal levels of NGFI-B mRNA were detected in all analyzed regions in Fischer and Lewis rats (Fig. 3*A*). In Lewis rats, a higher basal level of Nor1 mRNA was detected in cingulate and motor cortex (Figs. 3*B*, 4). In the other regions analyzed, no differences in Nor1 mRNA were detected. Nurr1 mRNA was detected at similar levels in claustrum in the two rat strains (data not shown).

NGFI-B, Nor1, and Nurr1 mRNA expression after chronic running

In Lewis rats, chronic running downregulated NGFI-B mRNA levels in cingulate, motor, and sensory cortex and downregulated

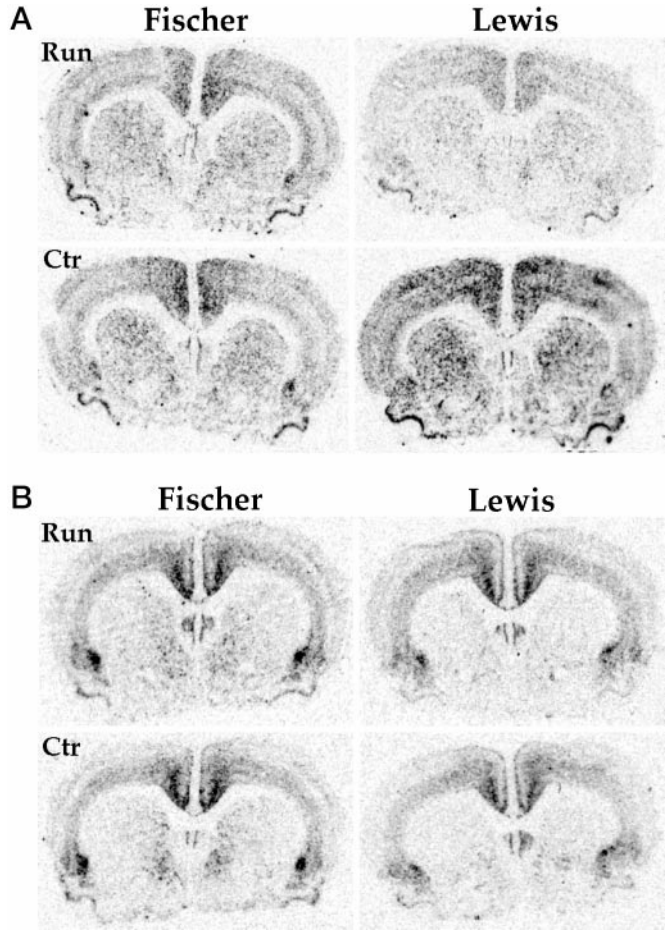

Figure 3. Film autoradiograms after *in situ* hybridization using 48-mer oligonucleotide DNA probes to detect mRNA distribution and regulation of NFGI-B (*A*) and Nor1 (*B*) mRNA levels in rats that were individually housed and had free access to running wheels for 30 d. Control rats were individually housed for 30 d without access to running wheels.

Nor1 mRNA in accumbens shell and core, cingulate, and motor cortex (Figs. 3*A*,*B*, 4). In forelimb regions of somatosensory cortex that had received chronic sensory stimulation, similar downregulation of NGFI-B and Nor1 mRNAs could not be detected (data not shown), as demonstrated at the level of sensory cortex as defined in Figure 1. In all other regions analyzed for both NGFI-B and Nor1 message, there were trends of downregulation. In Fischer rats, running had no effect on the levels of NGFI-B or Nor1 mRNA (Figs. 3*A*,*B*, 4). Running had no effect on Nurr1 mRNA in analyzed regions in either rat strain (data not shown).

NGFI-B, Nor1, and Nurr1 mRNA expression after chronic running and naloxone

Naloxone administration alone did not alter Nor1 mRNA levels in Lewis or Fischer rats (Fig. 5). In contrast, naloxone downregulated NGFI-B mRNA in a similar manner in the medial caudate putamen and cingulate cortex in both Fischer and Lewis rats (Fig. 5). In addition, naloxone downregulated NGFI-B mRNA in lateral caudate putamen, sensory, and motor cortex in the Lewis rat (Fig. 5). Naloxone had no effect on Nurr1 mRNA (data not shown). In Lewis rats, the running-induced downregulation of

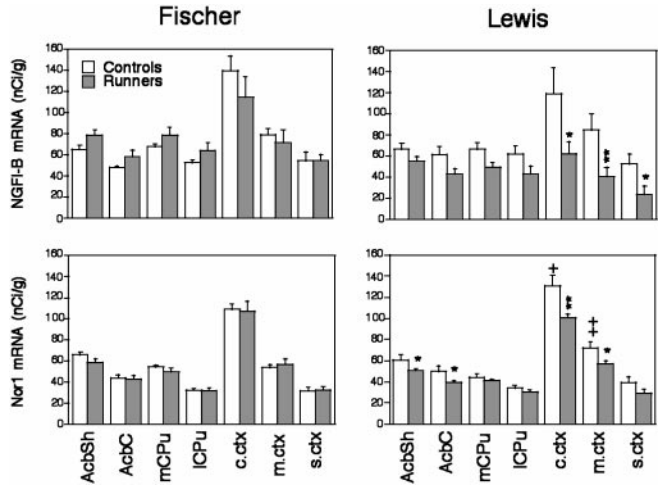

Figure 4. Relative levels of NGFI-B and Nor1 mRNA in control rats that were individually housed for 30 d without access to running wheels and compared with runners with access to running wheels. For abbreviations, see Figure 1. Values are means ± SEM ($n = 8$). $+p < 0.05$; $++p < 0.01$, significance for higher basal level in the indicated strain; $*p < 0.05$; $**p < 0.01$, indicates significantly lower levels of the respective mRNA after running.

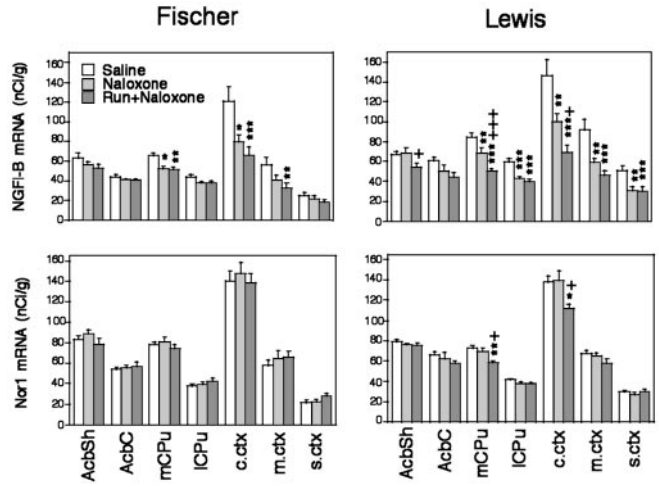

Figure 5. Relative levels of NGFI-B and Nor1 mRNA in saline-injected control animals (*Saline*) without access to running wheels, naloxone-treated (2 mg/kg, s.c) rats with (*Running + Naloxone*) and without (*Naloxone*) free access to running. The animals were killed 2 hr after injections. For abbreviations, see Figure 1. Values are means ± SEM ($n = 6–8$). $*p < 0.05$; $**p < 0.01$; $***p < 0.001$, indicates significant difference when comparing saline-injected control animals with naloxone-treated animals or animals with access to running wheels and naloxone. $+p < 0.05$; $++p < 0.01$; $+++p < 0.001$, indicates significant differences when comparing naloxone treated animals without access to running wheels with animals receiving naloxone with access to running wheels.

Nor1 mRNA was blocked by naloxone in the accumbens shell and core and motor cortex (Figs. 4, 5). Naloxone did not modify the running-induced changes in NGFI-B mRNA in any analyzed region (Figs. 4, 5). The relative downregulation of NGFI-B in all regions in the group of animals with free wheel access and given naloxone was in the range of the downregulation observed by running alone (Figs. 4, 5). It therefore appears that naloxone downregulation and running downregulation are not synergistic in terms of regulating NGFI-B levels.

DISCUSSION

In the present study, we have analyzed running behavior and regulation of mRNA encoding the nuclear orphan receptors NGFI-B and Nor1 in two rat strains with known differences in their stress responses and preferences for addictive behavior. The Lewis rats covered significantly longer daily running distances compared with the Fischer rats. As soon as the first day with free access to running wheels, Lewis rats ran markedly longer than Fischer rats. Lewis rats displayed an almost linear increase of running distance the first 14 d, after which they reached a plateau at which they remained or from which they decreased slightly. In contrast, Fischer rats did not seem to reach a plateau during the 30 d trial period. Instead, they increased their daily running distance throughout the experiment.

One reason for the discrepancy in running behavior could be that long-distance running might activate endogenous opioid systems and thus indirectly activate the same central monoamine pathways in the brain as those stimulated by drugs of abuse. Because Lewis rats more readily initiate a drug administrative behavior (Nestler, 1992), it is possible that the rewarding effects are greater in this rat strain. Rewarding effects of morphine are suggested to be mediated via activation of dopaminergic cells in the ventral tegmental area (VTA) leading to release of dopamine in nucleus accumbens. One mechanism for this could be a μ-receptor disinhibition mechanism via GABAergic interneurons, which under normal conditions blocks activity of dopaminergic cells in the VTA (Johnson and North, 1992). β-endorphins function as endogenous agonists for opioid μ receptors, and it is possible that β-endorphins could also activate dopaminergic neurons in the VTA via a mechanism similar to that of morphine. By analogy, it could be more rewarding for Lewis rats to run than for Fischer rats, which would explain the behavior results in our experiments.

Another possible explanation for the different running patterns in Lewis versus Fischer rats might be differences in stress sensitivity or spontaneous locomotor activity. However, when placed in activity cages or during open-field tests, Fischer rats display more locomotor activity than the Lewis rats (Chaouloff et al., 1995). In our experiments using running wheels, Lewis rats ran considerably more than Fischer rats as soon as during the first 24 hr, and in the light of spontaneous locomotor data, it appears as if the higher running levels in Lewis rats cannot be attributed to higher spontaneous locomotor activity.

Chronic voluntary running was associated with a statistically significant decrease of NGFI-B mRNA in cingulate, motor, and sensory cortex and a trend toward a downregulation in the other regions analyzed in the Lewis rat. Nor1 was also downregulated with statistical significance in accumbens core and shell, as well as cingulate and motor cortex, with a trend toward downregulation in the other investigated brain regions in the Lewis rat. In the Fischer rat, running had no effect in any analyzed brain region. In other studies, social stress has been reported to be associated with increased levels of c-fos in cortex cinguli and amygdala (Kollack-Walker et al., 1997). c-fos and NGFI-B are co-induced in hypothalamus in several models of stress (Umemoto et al., 1997; Ogilvie et al., 1998). Rats are nocturnal animals, and it is possible that the decreased levels of NGFI-B and Nor1 messages in cerebral cortex, accumbens, and caudate putamen in the running Lewis rat might reflect a state of decreased functional activity at the time of dissection (12:00 P.M.) in brain regions involved in stress responses, motor function, and reward. It is possible that these brain regions had been adapted to a state of high activity during chronic running and that the lower levels of NGFI-B and Nor1 detected could reflect an adaptation to this. In contrast, in the Fischer rats, which do not develop the same excessive running behavior, no such downregulation of NGFI-B or Nor1 was observed. It is, however, important to note that the animals in our study were dissected after continuous free access to running wheels and that the dissection was performed during their resting phase of the day. At this time, the CSF endorphin levels are still increased (Hoffmann et al., 1990b), and consequently the animals cannot be regarded as experiencing an endorphin withdrawal state. In fact, endorphin levels are maintained at a high level for 48 hr after blocking access to running wheels (Hoffmann et al., 1990b).

Chronic administration of morphine causes physical dependence, and by blocking μ-receptors, the opioid receptor antagonist naloxone precipitates a withdrawal that is manifested by diarrhea, seizures, and weight loss. To analyze μ-receptor-mediated effects in our model, we administered naloxone at a dose that blocks increase of pain thresholds after chronic running (Shyu et al., 1982) but not the κ-mediated effects on blood pressure after rhythmic muscle activation (Hoffmann et al., 1990a). However, we could not detect any obvious signs of physical withdrawal. The downregulation of Nor1 mRNA caused by running was in some instances attenuated by naloxone, whereas naloxone did not modulate the running-induced NGFI-B downregulation. Instead, naloxone alone downregulated NGFI-B in medial and lateral striatum, as well as in cortex cinguli, in both Fischer and Lewis rats. The effects of naloxone suggest that the running-induced downregulation of NGFI-B is not acutely mediated via endogenous opioids, whereas endogenous opioids might contribute to the regulation of Nor1 mRNA.

Acute treadmill activity increases extracellular dopamine levels in nucleus accumbens in the rat (Wilson and Marsden, 1995). Chronic running increases CSF β-endorphins (Hoffmann et al., 1990b) and modulates turnover of central brain monoamines (Elam et al., 1987) involved in brain mechanisms of stress, as well as psychiatric conditions of drug addiction and affective disorders. In spontaneously hypertensive rats, chronic running leads to both less aggressive behavior and decreased hyperexplorative behavior (Hoffmann et al., 1987). Dopamine is believed to be the mediator of central reward mechanisms via the dopaminergic cell group in the VTA, which projects to nucleus accumbens in the ventral forebrain (Koob, 1992; Nestler, 1992). In fact, most drugs that are abused by humans are also self-administered by rats, and it has been documented that acute administration of cocaine, amphetamine, morphine, nicotine, and ethanol all trigger release of dopamine in nucleus accumbens (Di Chiara and Imperato, 1988). In addition, we have demonstrated that compulsive running in Lewis rats and cocaine administration both increase levels of dynorphin mRNA in striatum, suggesting a common mechanism of regulation (our unpublished observations). Because chronic running modulates central dopamine levels, running could possibly also effect brain reward pathways.

Interestingly, after withdrawal from addictive drugs such as amphetamine, cocaine, opioids, nicotine, or ethanol, subjects suffer psychological symptoms such as depression and anxiety, which are believed to play a major role in motivation, for increased drug intake, and relapse (Koob and Le Moal, 1997). It is possible that the psychological features of withdrawal from addictive drugs have a common molecular and neurobiological background, ultimately allowing application of a common therapeutic program. Joggers frequently express positive mood changes ("joggers'

high"), with reduced levels of depression and anxiety (Bahrke, 1979; Greist et al., 1979; Sonstroem and Morgan, 1989). In fact, exercise appears to be as efficient as antidepressant drug therapy for selected types of anxiety and depression (Bahrke, 1979; Greist et al., 1979; Sonstroem and Morgan, 1989). The documented changes caused by chronic running in animal models involve CSF β-endorphins and central monoamine turnover, which might underlie the beneficial sense of well being caused by running.

In this study, we show that the addiction-prone Lewis rat developed a higher preference for running compared with the less addiction-prone Fischer rat. We therefore speculate on common mechanisms in development of drug-addictive behavior and compulsive exercise. One hypothesis is that the Lewis rat by running activates the same neurobiological circuits as those activated by drugs of abuse. By continuing to run, the animal does not enter the psychological withdrawal phase associated with anxiety and depression. In fact, forced withdrawal from running in the spontaneous hypertensive rat leads to aggressive behavior that possibly could be similar to the psychological withdrawal from addictive drugs. In a first step to characterize the molecular background of the voluntary running behavior, we analyzed the levels of the nuclear orphan receptors NGFI-B and Nor1 mRNAs, which we found were both downregulated by chronic running. However, further studies are necessary to clarify the role of NGFI-B and Nor1 in these processes. We conclude that an addiction-prone rat strain develops compulsive running that is associated with a temporally related downregulation of important transcription factors of the NGFI-B family. Compulsive running and drug addiction may share certain, but not all, underlying molecular mechanisms.

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