ΔFosB Regulates Wheel Running

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ΔFosB is a transcription factor that accumulates in a region-specific manner in the brain after chronic perturbations. For example, repeated administration of drugs of abuse increases levels of ΔFosB in the striatum. In the present study, we analyzed the effect of spontaneous wheel running, as a model for a natural rewarding behavior, on levels of ΔFosB in striatal regions. Moreover, mice that inducibly overexpress ΔFosB in specific subpopulations of striatal neurons were used to study the possible role of ΔFosB on running behavior. Lewis rats given *ad libitum* access to running wheels for 30 d covered what would correspond to ~10 km/d and showed increased levels of ΔFosB in the nucleus accumbens compared with rats exposed to locked running wheels. Mice that overexpress ΔFosB selectively in striatal dynorphin-containing neurons increased their daily running compared with control littermates, whereas mice that overexpress ΔFosB predominantly in striatal enkephalin-containing neurons ran considerably less than controls. Data from the present study demonstrate that like drugs of abuse, voluntary running increases levels of ΔFosB in brain reward pathways. Furthermore, overexpression of ΔFosB in a distinct striatal output neuronal population increases running behavior. Because previous work has shown that ΔFosB overexpression within this same neuronal population increases the rewarding properties of drugs of abuse, results of the present study suggest that ΔFosB may play a key role in controlling both natural and drug-induced reward.

Key words: nucleus accumbens; striatum; locomotion; exercise; natural reward; behavioral addiction; compulsive; drugs of abuse

ΔFosB belongs to the Fos family of transcription factors and is derived from the fosb gene via alternative splicing. Unlike all other Fos-like proteins, which have short half-lives, the 35 and 37 kDa isoforms of ΔFosB accumulate in a region-specific manner in the brain after a variety of chronic perturbations, presumably because of the very high stability of these isoforms (Hope et al., 1994a; Chen et al., 1997; Nestler et al., 1999). The regulation of ΔFosB in striatal regions after repeated administration of drugs of abuse has been especially well studied (Hope et al., 1994b; Moratalla et al., 1996; Chen et al., 1997; Nestler et al., 1999). The mesolimbic dopamine pathway has a central role in drug reward (Koob et al., 1998). It originates in the ventral tegmental area of the midbrain and terminates in the ventral part of the striatum, called the nucleus accumbens. Acute administration of any of several drugs of abuse transiently induces several Fos family proteins in the nucleus accumbens and in the dorsal striatum. These proteins form heterodimers with Jun family proteins to form activator protein-1 (AP-1) transcription factor complexes with short half-lives. In contrast, after repeated drug treatment, induction of these immediate early gene products declines and, instead, there is a gradual accumulation of the stable ΔFosB isoforms. ΔFosB heterodimerizes predominantly with JunD and to a lesser extent with JunB (Hiroi et al., 1998; Perez-Otano et al., 1998) to form long-lasting AP-1 complexes in specific brain regions. It has been proposed that these long-lasting AP-1 complexes mediate some of the long-term effects of drugs of abuse on brain reward pathways that underlie addiction (Nestler et al., 2001).

Behavioral studies suggest that wheel running in rodents is rewarding. This assumption is based on experiments showing that rats lever-press for access to running wheels and also develop conditioned place preference to an environment associated with the aftereffects of wheel running (Iversen, 1993; Belke, 1997; Lett et al., 2000). Moreover, rats that run long distances daily exhibit withdrawal signs, such as increased aggression, when access to the running wheels is denied (Hoffmann et al., 1987). Surveys among highly committed human runners suggest that running is an addictive behavior for many individuals (Rudy and Estok, 1989; Chapman and De Castro, 1990; Furst and Germone, 1993). Indeed, running displays many of the criteria included in the Diagnostic Statistical Manual (American Psychiatric Association, 1994) for the diagnosis of addiction.

The goal of the present study was to investigate whether levels of ΔFosB are altered by a natural rewarding behavior such as running and whether inducible overexpression of ΔFosB in striatal regions might regulate running behavior. We show here that, like drugs of abuse, chronic running induces ΔFosB in the nucleus accumbens; in addition, the overexpression of ΔFosB in the two different subsets of striatal projection neurons has opposite effects on wheel running. The data reveal striking similarities between addictive drugs and wheel running and suggest an important role for ΔFosB in regulating both natural and drug-induced rewards.

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MATERIALS AND METHODS

Animals. Male Lewis rats (Møllegaard Breeding Center, Skansved, Denmark) weighing 250 gm at the onset of the experiment were used. The rats had access *ad libitum* to water, food, and running wheels. They were on a 12 hr light/dark cycle, with lights on at 10 A.M. and lights off at 10 P.M. Cages (43 × 22 × 20 cm) contained a running wheel with a diameter of 34 cm; hence, one revolution corresponds to 1.07 m. After 4 weeks of voluntary wheel running, the rats were killed by decapitation, and tissues were taken for Western blotting or perfused with fixative and processed for immunohistochemistry and *in situ* hybridization.

Two lines of bitransgenic mice that can inducibly overexpress Δ*FosB* selectively in striatal regions under the control of the tetracycline gene regulation system were also used (Chen et al., 1998). In one line, called 11A, Δ*FosB* is inducibly overexpressed solely in striatal projection neurons that express the neuropeptide dynorphin after removal of doxycycline (Kelz et al., 1999). In the other line, called 11B, Δ*FosB* is inducibly overexpressed predominantly in striatal projection neurons that express the neuropeptide enkephalin after removal of doxycycline, although some expression is seen in dynorphin neurons as well. Controls and Δ*FosB*-overexpressing mice are littermates within each line (11A and 11B) and have the same bitransgenic construct, which can be activated by removal of doxycycline. All mice were conceived and raised on the tetracycline derivative doxycycline at a dose of 100 μg/ml in the drinking water. As adults, one-half of the resulting litters were maintained on doxycycline (controls); the other half were removed from doxycycline (Δ*FosB* overexpressers) for the rest of the experiment. Six weeks after removal of doxycycline, at which time Δ*FosB* expression is known to be maximal (Chen et al., 1998; Kelz et al., 1999), the running wheels were unlocked for both mice on tetracycline (controls) and mice on tap water (Δ*FosB* overexpressers), and voluntary running started. To rule out the possibility that doxycycline itself affected wheel-running behavior, we analyzed wheel running in C57BL/6 mice (Charles River, Uppsala, Sweden) treated with 100 μg/ml doxycycline for 6 weeks before being allowed access to the running wheels. The mice were then placed in the cages with *ad libitum* access to the running wheels and remained on tetracycline during the entire experiment. The control group received normal drinking water during the entire experiment. Mouse cages (22 × 16 × 14 cm) contained a running wheel with a diameter of 12.4 cm; hence, one revolution corresponds to 0.39 m. Running data from both rats and mice were sampled every 30 min using customized computer software.

Western blotting. Brains were removed rapidly from decapitated rats and chilled in ice-cold physiological buffer. Punches with a diameter of 2 mm were used to sample tissues from the nucleus accumbens and the medial and lateral caudate putamen in 1-mm-thick coronal slices of brain at the level of bregma 0.7–1.7 mm (Paxinos and Watson, 1997). Brain samples were homogenized in 1% SDS, and protein determinations were made using the method of Lowry. Homogenates containing between 5 and 50 μg of protein were loaded onto SDS-polyacrylamide gels and subjected to electrophoresis as described. A rabbit anti-Fos antibody (1:4000; M. J. Iadarola, National Institutes of Health, Bethesda, MD) or anti-FosB (N-terminal) antibody (1:4000; Santa Cruz Biotechnology, Santa Cruz, CA) was used for detection of Δ*FosB*. Proteins were detected using horseradish peroxidase-conjugated IgG antibodies (1:2000; Vector Laboratories, Burlingame, CA) followed by chemiluminescence (DuPont NEN, Boston, MA). Levels of immunoreactivity (IR) were quantified on a Macintosh-based image analysis system, and levels of protein in the experimental samples were compared with those of controls. Blots were stained by amido black to confirm equal loading and transfer of the gels. Blots were also immunolabeled for 68 kDa neurofilament protein, which did not show differences between the experimental and control groups (data not shown).

Immunohistochemistry. Lewis rats that had run for 4 weeks and controls with locked wheels were deeply anesthetized with pentobarbital and perfused intracardially with 50 ml of Ca^{2+}-free Tyrode's solution (room temperature) including 0.1 ml of heparin. This was followed by 250 ml of fixative (4% paraformaldehyde and 0.4% picric acid in 0.16 M PBS, pH 7.4, at room temperature). Brains were divided and kept in fixative for 1 hr and subsequently rinsed in 0.1 M PBS with 10% sucrose and 0.1% sodium azide several times over 24 hr at 4°C for cryoprotection. The brains were frozen, and 14 μm coronal sections were collected at levels ranging between bregma 0.70 and 1.70 mm. Sections were rinsed three times for 10 min in PBS before overnight incubation (4°C in moisture chamber) with primary polyclonal anti-FosB (N-terminal) antibody (1:500; Santa Cruz Biotechnology) in 0.3% Triton-PBS (150 μl per section). This was followed by three rinses with PBS for 10 min before incubation for 1 hr at room temperature with the secondary biotinylated anti-rabbit IgG antibody (1:200; Vector Laboratories) in 0.3% Triton-PBS (150 μl per section). Another three rinses in PBS for 10 min were performed before the avidin–biotin complex was added (1:100 and 1:100, respectively, in 0.1 M PBS; 150 μl per section). After three 10 min rinses, the complex was visualized after a 7 min incubation with the substrate according to the manufacturer's protocol (Vector Laboratories). Sections were subsequently rinsed three times for 5 min.

In situ *hybridization.* For combined immunohistochemistry and *in situ* hybridization experiments, brain sections that had been processed for immunohistochemistry were immediately subjected to *in situ* hybridization, which was performed essentially as described previously (Seroogy et al., 1989; Dagerlind et al., 1992). Forty-eight mer DNA oligonucleotide probes specific for dynorphin (296–345) (Douglass et al., 1989) and enkephalin (235–282) (Zurawski et al., 1986) mRNAs were radioactively labeled with [α-^{35}S]dATP (DuPont NEN) in their 3′ ends using terminal deoxynucleotidyl transferase (Invitrogen, San Diego, CA) to a specific activity of ~1×10^9 cpm/mg. 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 sulfate, 0.06 M dithiothreitol, and 0.1 mg/ml sheared salmon sperm DNA. Hybridization was performed for 18 hr in a humidified chamber at 42°C. After hybridization, the sections were rinsed four times for 20 min each in 1× SSC at 60°C. Thereafter, the sections were rinsed in autoclaved water for 10 sec, dehydrated in alcohol, and air-dried. Finally, NTB2 nuclear track emulsion (diluted 1:1 with water; Kodak, Rochester, NY) was applied by dipping. After 2–4 weeks of exposure, the slides were developed with D19 (Kodak) and fixed with Unifix (Kodak).

Counts of cells positive for *FosB*-IR and cells colocalizing FosB-IR and dynorphin mRNA or enkephalin mRNA in rats after 4 weeks of running ($n = 8$) and in controls ($n = 8$) were performed on one slide per animal by an independent observer blinded to the experimental design. Analysis was performed at the level of bregma 1.2 mm (Paxinos and Watson, 1997).

Statistical procedures. To analyze the difference in Δ*FosB* levels between controls and runners in the Western blotting and immunohistochemistry experiments, *t* tests were performed. The effect of overexpression of Δ*FosB* on running behavior in the transgenic mice was analyzed using a two-way ANOVA with repeated measurements, analyzing within-group and between-group effects (Statistica version 99; StatSoft, Tulsa, OK).

RESULTS

Regulation of Δ*FosB* in nucleus accumbens by wheel running

Lewis rats placed in cages with running wheels increased their amount of daily running linearly until day 13, when they stabilized at 10.210 ± 590 m/d (mean ± SEM). This level was roughly maintained through day 32, when the animals were used for biochemical analysis. During the last 4 d, the rats ran 8.910 ± 900 m/d. This running behavior in Lewis rats is similar to that observed previously (Werme et al., 1999). Subsequently, levels of Δ*FosB* were analyzed by Western blotting in the nucleus accumbens and in the medial and lateral caudate putamen in running ($n = 7$) and control ($n = 7$) rats. As shown in Figure 1, wheel running increased Δ*FosB* levels of the 37 and 35 kDa isoforms in the nucleus accumbens ($p < 0.05$). In contrast, there was no difference in Δ*FosB* levels between runners and controls in the medial or lateral caudate putamen (data not shown).

Immunohistochemistry revealed the presence of Δ*FosB*-positive cells in the nucleus accumbens of control ($n = 8$) and running ($n = 8$) rats. Counts of Δ*FosB*-positive cells in the core and shell revealed an increase in the number of cells expressing Δ*FosB*-IR in the core ($p < 0.05$) but not in the shell of nucleus accumbens after running (Fig. 2). Combined immunohistochemistry for Δ*FosB*-IR and *in situ* hybridization for enkephalin or dynorphin mRNA in the nucleus accumbens was subsequently

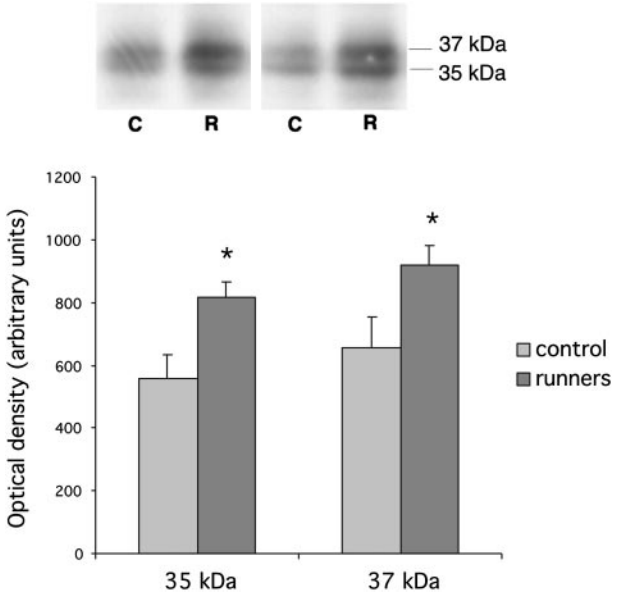

Figure 1. Regulation of Δ*FosB* by wheel running. Levels of the 35–37 kDa isoforms of Δ*FosB* were measured in the nucleus accumbens using Western blotting in control rats (*C*) and in rats that underwent 4 weeks of voluntary wheel running (*R*). *Top*, Representative *lanes* from the blots. Data are expressed as mean ± SEM (both groups, $n = 7$). $^*p < 0.05$.

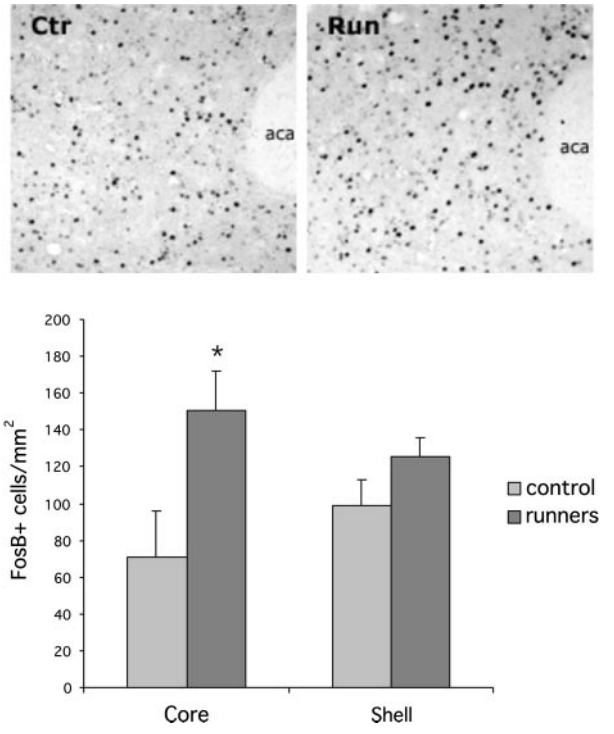

Figure 2. Wheel running affects the number of Δ*FosB*-positive cells in the nucleus accumbens. *Top*, Representative photomicrographs of rat brain sections demonstrating the increase in the number of Δ*FosB*-positive cells in the nucleus accumbens core when runners (*Run*) were compared with controls (*Ctr*). *aca*, Anterior commissure anterior. *Bottom*, Bar graph of counts of cells positive for Δ*FosB*-IR in the medial aspects of the core and shell of the nucleus accumbens in control rats and in rats that underwent 4 weeks of voluntary wheel running. Data are expressed as mean ± SEM (both groups, $n = 8$). $^*p < 0.05$.

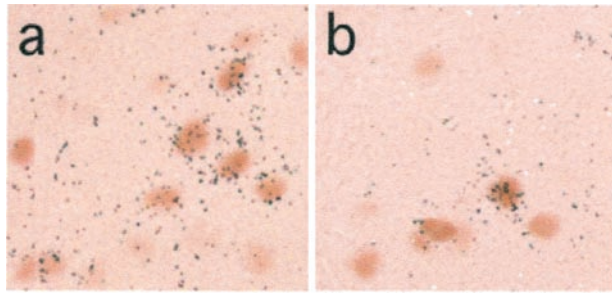

Figure 3. Cellular specificity of Δ*FosB* induction by wheel running. Representative photomicrographs of rat brain sections from eight individuals demonstrating colocalization of Δ*FosB*-IR (*brown stained nuclei*) and dynorphin mRNA (*black grains*) (*a*) or Δ*FosB*-IR and enkephalin mRNA in the nucleus accumbens core (*b*).

used to identify the cell type within this brain region in which Δ*FosB* is induced by running (Fig. 3). While the number of cells expressing both dynorphin mRNA and FosB-IR was higher in runners ($n = 8$) than in controls ($n = 8$) (Table 1), the mean number of cells expressing both enkephalin mRNA and FosB-IR in runners was lower than in controls (Table 1). These effects were apparent in the core subdivision of this brain region (Table 1). These results indicate that the induction of Δ*FosB* by running occurs predominantly in the dynorphin-containing subset of nucleus accumbens neurons.

Effect of Δ*FosB* on wheel running

To study a possible role of Δ*FosB* in regulating wheel running, we used two lines of bitransgenic mice that inducibly overexpress Δ*FosB* within striatal regions of adult animals (Chen et al., 1998; Kelz et al., 1999). The bitransgenic 11A line can inducibly overexpress Δ*FosB* solely within dynorphin-containing neurons in the striatum (Kelz et al., 1999), whereas the bitransgenic 11B line can inducibly overexpress Δ*FosB* predominantly in enkephalin-containing neurons in this region, with some expression seen in dynorphin neurons as well (Fig. 4). Both lines of mice were conceived and raised on doxycycline to keep Δ*FosB* expression turned off (Fig. 4) (Kelz et al., 1999), and one-half of the littermates were removed from doxycycline as adults to turn on Δ*FosB* expression.

11A mice that overexpress Δ*FosB* (no doxycycline) ($n = 7$) were found to increase their daily running distance over the first 3 weeks compared with the littermate controls (given doxycycline) ($n = 8$), which showed a plateau in their rate of running after 2 weeks (Fig. 5*A*). In striking contrast, 11B mice that overexpressed Δ*FosB* ($n = 7$) showed considerably less running activity during weeks 2 and 3 than their littermate controls ($n = 6$) (Fig. 5*B*). To investigate the possibility that doxycycline itself might alter running behavior, we compared wheel running of C57BL/6 mice with and without doxycycline in their drinking water. No difference between the groups was found (data not shown).

DISCUSSION

In this study, we show that like repeated exposure to drugs of abuse, chronic wheel running, a natural rewarding behavior, induces Δ*FosB* in the nucleus accumbens, a critical part of the reward pathways of the brain. We also show that overexpression of Δ*FosB* in striatal dynorphin neurons of adult animals increases running behavior, whereas Δ*FosB* expression primarily in striatal enkephalin neurons has the opposite effect. These data support the view that Δ*FosB* is critically involved in long-term effects of

Table 1. ΔFosB in dynorphin and enkephalin cells in nucleus accumbens

	Control		Runners	
	Core	Shell	Core	Shell
ΔFosB + dynorphin	+	+	++	+
ΔFosB + enkephalin	+++	+	+	+

Distribution and rating of cells that colocalize dynorphin mRNA and FosB-IR and enkephalin and FosB-IR in rat nucleus accumbens core and shell in runners ($n = 8$) and control ($n = 8$). The rating of + indicates 0–10 colocalizing cells/mm^2, ++ indicates 10–20 colocalizing cells/mm^2, and +++ indicates >20 colocalizing cells/mm^2. Analysis was performed by an independent observer on coded slides.

natural and drug-induced rewards and underscore the important role of ΔFosB in the regulation of striatal function.

Similar molecular responses to drugs of abuse and running

Drugs of abuse as diverse as psychostimulants, opiates, alcohol, nicotine, and phencyclidine increase levels of ΔFosB in the nucleus accumbens (Hope et al., 1994b; Nye et al., 1995; Nye and Nestler, 1996; Nestler et al., 1999), and here we show that chronic running behavior results in a similar response. Chronic cocaine and running induce additional common adaptations, for example, induction of dynorphin mRNA in certain regions of the striatum (Werme et al., 2000). As noted previously for cocaine (Hiroi et al., 1997), the induction of ΔFosB by running is stronger in the core than in the shell division of the nucleus accumbens. However, ΔFosB induction by running is restricted to the nucleus accumbens, whereas drugs of abuse induce the protein in the caudate putamen as well. Previous studies have demonstrated that ΔFosB is expressed solely in projection neurons of the striatum, and that chronic cocaine increases ΔFosB preferentially in the subpopulation of projection neurons that express dynorphin (Moratalla et al., 1996). In the present study, by use of combined immunohistochemistry and *in situ* hybridization on the same tissue sections, we showed that wheel running also induces ΔFosB preferentially within dynorphin neurons.

The finding that drug reward and a natural reward induce the same molecular adaptation (induction of ΔFosB) within the same neuronal cell type suggests that the two may act via some common mechanism. One plausible common mechanism is increased dopaminergic transmission to the nucleus accumbens. Running and acute administration of addictive drugs increases extracellular levels of dopamine in this brain region (Freed and Yamamoto, 1985; Di Chiara and Imperato, 1988; Wilson and Marsden, 1995).

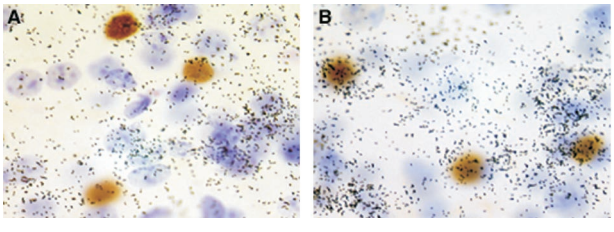

Figure 4. Expression of ΔFosB in 11B mice. Brain sections were analyzed for ΔFosB-IR (*brown-stained nuclei*) followed by *in situ* hybridization for dynorphin mRNA (*A*) or enkephalin mRNA (*B*) (*black grains*). Note the preferential expression of ΔFosB-IR in the enkephalin-positive but not the dynorphin-positive cells. Of 214 ΔFosB-positive cells counted in three 11B mice, 73 ± 11% were also enkephalin positive, and 22 ± 6% were also dynorphin positive. No double-labeling was seen between ΔFosB and interneuron markers.

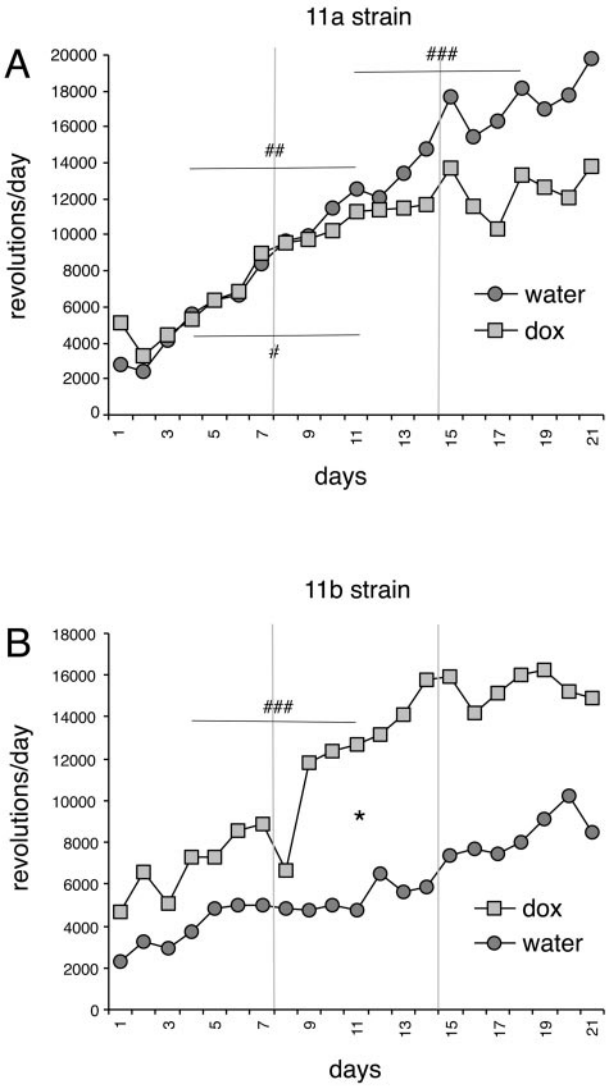

Figure 5. Effect of ΔFosB overexpression on wheel running behavior in bitransgenic mice. *A*, Bitransgenic mice drinking tap water have inducible overexpression of ΔFosB in striatal dynorphin neurons (*water*) and showed increased running (distance per day) for the first 3 weeks of access to running wheels. In contrast, genetically identical littermate controls with doxycycline in their drinking water that do not overexpress ΔFosB (*dox*) showed increased running for the first 2 weeks only. *B*, Another line of the bitransgenic strain of mice, called 11B, with inducible overexpression of ΔFosB primarily in striatal enkephalin neurons (*water*) showed dramatically less running during their weeks 2 and 3 compared with genetically identical littermates that do not overexpress ΔFosB (*dox*). # indicates an increase in running (distance per week) within a group. * indicates a difference in running between the ΔFosB overexpressers (*water*) and controls (*dox*). *Vertical lines* indicate borders between weeks 1 and 2, as well as weeks 2 and 3. *Horizontal lines* with the # symbol describe statistical differences between weekly running within a group. Data are expressed as mean (11A dox, $n = 8$; 11A water, $n = 7$; 11B dox, $n = 6$; 11B water, $n = 7$). $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.001$; $^{*}p < 0.05$.

Repeated treatment with the D_1 dopamine receptor agonist (+/−)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepin hydrobromide alone or in combination with the D_2 receptor agonist quinpirole will increase levels of ΔFosB in the nucleus accumbens and dorsal striatum (Nye et al., 1995). Psychostimulant addictive drugs such as cocaine and amphetamine, which are indirect dopamine agonists, also increase ΔFosB levels

in striatal regions (Jaber et al., 1995; Nye et al., 1995). In addition, chronic administration of the specific dopamine transporter antagonist 1-[2-(bis[4-fluorophenyl]methoxy)ethyl]-4-(3-hydroxy-3-phenylpropyl) piperazinyl decanoate, but not of serotonin- or norepinephrine-selective transporter inhibitors, induces Δ*FosB* in these brain regions (Nye et al., 1995). These findings demonstrate that induction of Δ*FosB* in the striatum after various treatments is dependent on dopamine.

Opposite effects of Δ*FosB* overexpression in striatal dynorphin versus enkephalin neurons on wheel-running behavior

The bitransgenic mice with Δ*FosB* overexpression that is induced by doxycycline removal from adult animals show no overt developmental abnormalities. In mice in which Δ*FosB* overexpression is selective for striatal dynorphin neurons, running behavior increased during the first 3 weeks of running, instead of the first 2 weeks as seen for control littermates. In marked contrast, mice overexpressing Δ*FosB* primarily in striatal enkephalin neurons ran less than their control littermates during weeks 2 and 3 of running. Interestingly, the two lines of bitransgenic mice studied here also show different behavioral responses to drugs of abuse. Whereas overexpression of Δ*FosB* in dynorphin neurons increases the rewarding effects of cocaine and morphine (Kelz et al., 1999; Nestler et al., 2001), overexpression of Δ*FosB* primarily in the enkephalin neurons does not alter the rewarding effects of these drugs.

The opposite effects on running behavior seen in the two lines of mice could be explained by the differential circuitry of these two distinct subpopulations of striatal neurons. More than 90% of striatal neurons are medium spiny projection neurons that use GABA as a neurotransmitter. Approximately one-half of these neurons also express high levels of dynorphin and substance P (and to a certain extent the D_1 dopamine receptor) (Gerfen et al., 1990; Le Moine et al., 1991) and project directly to the midbrain. The other half express high levels of enkephalin (and D_2 dopamine receptor) (Gerfen et al., 1990; Le Moine et al., 1990) and project indirectly to the midbrain via the globus pallidus and subthalamic nucleus. Activation of the direct pathway increases locomotion, whereas activation of the indirect pathway decreases locomotion. Thus, the reciprocal changes in running behavior exhibited by the two lines of Δ*FosB*-overexpressing mice used in these experiments could reflect Δ*FosB*-induced changes in the excitability of the direct versus the indirect pathway. Along these lines, it is interesting to speculate that the reduction in wheel running seen in mice overexpressing Δ*FosB* primarily in enkephalin neurons may be consistent with the fact that first-generation antipsychotic drugs, which decrease locomotor activity, induce Δ*FosB* selectively within this neuronal subpopulation (Hiroi and Graybiel, 1996; Atkins et al., 1999).

Target genes regulated by Δ*FosB*

The effects of Δ*FosB* on neuronal function are presumably mediated via the regulation of other genes. Given that many genes contain consensus sites for AP-1 complexes in their promoter regions, it is likely that the actions of Δ*FosB* on neurons involve complex effects on numerous genes. Only a few have been identified to date. The AMPA glutamate receptor subunit 2 (GluR2) is upregulated by Δ*FosB* in the nucleus accumbens, an effect not seen in the dorsal striatum (Kelz et al., 1999). Cyclin-dependent kinase 5 (Cdk5) is upregulated in both the nucleus accumbens and dorsal striatum (Bibb et al., 2001). These effects could be mediated via AP-1 sites present in the promoter regions of these genes (Brene et al., 2000; Chen et al., 2000). Regulation of GluR2 would be expected to alter the electrical excitability of striatal neurons by changing their AMPA receptor sensitivity. Regulation of Cdk5 might also alter the excitability of these neurons through a pathway involving dopamine and cAMP-regulated phosphoprotein-32, which is highly enriched in striatal medium spiny neurons (Brene et al., 1994; Bibb et al., 1999). However, further work is needed to identify the precise molecular pathways by which Δ*FosB*, through changes in the expression of other genes, alters the functional state of striatal dynorphin and enkephalin neurons.

Conclusions

The findings that similar molecular adaptations occur in the nucleus accumbens in natural and drug-induced reward situations suggest that common neurobiological mechanisms may control both types of rewarding behaviors. One core similarity between these behaviors is their addictive nature. Δ*FosB* is induced by both behaviors and enhances both behaviors when independently overexpressed in striatal dynorphin neurons. Perhaps Δ*FosB*, when expressed in these neurons, sensitizes a neural circuit related to compulsive behavior. Although speculative, the increasing knowledge about Δ*FosB* suggests that it, or the various molecular pathways it regulates, could be a suitable target for the development of pharmacological treatments for a range of disorders. Examples of these could be compulsive behaviors, including not only drug addiction but also eating disorders, pathological gambling, excessive exercise, and perhaps even obsessive-compulsive disorder.

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