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Overexpression of Δ FosB Is Associated With Attenuated Cocaine-Induced Suppression of Saccharin Intake in Mice

Christopher S. Freet¹, Cathy Steffen², Eric J. Nestler², and Patricia S. Grigson¹

¹ Department of Neural and Behavioral Sciences, Pennsylvania State University College of Medicine

² Department of Psychiatry and Neuroscience, University of Texas Southwestern Medical Center

Abstract

Rodents suppress intake of saccharin when it is paired with a drug of abuse (Goudie, Dickinson, & Thornton, 1978; Risinger & Boyce, 2002). By the authors' account, this phenomenon, referred to as reward comparison, is thought to be mediated by anticipation of the rewarding properties of the drug (P. S. Grigson, 1997; P. S. Grigson & C. S. Freet, 2000). Although a great deal has yet to be discovered regarding the neural basis of reward and addiction, it is known that overexpression of Δ FosB is associated with an increase in drug sensitization and incentive. Given this, the authors reasoned that overexpression of Δ FosB should also support greater drug-induced devaluation of a natural reward. To test this hypothesis, NSE-tTA $\times$ TetOp- Δ FosB mice (Chen et al., 1998) with normal or overexpressed Δ FosB in the striatum were given access to a saccharin cue and then injected with saline, 10 mg/kg cocaine, or 20 mg/kg cocaine. Contrary to the original prediction, overexpression of Δ FosB was associated with attenuated cocaine-induced suppression of saccharin intake. It is hypothesized that elevation of Δ FosB not only increases the reward value of drug, but the reward value of the saccharin cue as well.

Keywords

reward comparison; natural rewards; transgenic mice; CTA; intake

Δ FosB is a member of the Fos family of transcription factors that has received a great deal of attention as a possible molecular switch for the long-term neuronal plasticity observed in drug addiction (McClung et al., 2004; Nestler, Barrot, & Self, 2001; Nestler, Kelz, & Chen, 1999). Δ FosB can homodimerize (Jorissen et al., 2007) or heterodimerize with JunD (and to a lesser extent, JunB; Hiroi et al., 1998; Perez-Otano, Mandelzys, & Morgan, 1998) to form activator protein-1 complexes (Chen et al., 1995; Curran & Franza, 1988; Nestler et al., 2001). Activator protein-1, then, binds at the activator protein-1 consensus site (TGAC/GTCA) to promote or inhibit transcription of various genes including, but not limited to, dynorphin, the AMPA glutamate receptor subunit GluR2, cyclin-dependent kinase 5, and nuclear factor kappa B (Chen, Kelz, Hope, Nakabeppu, & Nestler, 1997; Dobrzanski et al., 1991; Nakabeppu & Nathans, 1991; Yen, Wisdom, Tratner, & Verma, 1991). In the nucleus accumbens, elevation of Δ FosB inhibits transcription of dynorphin (McClung et al., 2004, but see Andersson, Westin, & Cenci, 2003) but promotes transcription of GluR2 (Kelz & Nestler, 2000), cyclin-dependent kinase 5 (McClung & Nestler, 2003), and nuclear factor kappa B (Ang et al., 2001). Manipulation of many of these genes (and/or their products) has been found to influence

Correspondence concerning this article should be addressed to Christopher S. Freet, Department of Neural and Behavioral Sciences, Pennsylvania State University College of Medicine, 500 University Drive, H181, Hershey, PA 17033. csf5@psu.edu.
Eric J. Nestler is currently affiliated with Mount Sinai School of Medicine, New York, New York.

sensitivity to drugs of abuse. For example, overexpression of GluR2 using viral-mediated gene transfer in rats, or blockade of dynorphin by the κ -receptor antagonist nor-BNI in mice, increases the rewarding effects of cocaine and morphine, respectively (Kelz et al., 1999; Zachariou et al., 2006).

A number of factors can elevate Δ FosB in the brain, and the elevation can be region specific. Chronic stress, antipsychotic drugs, and drugs of abuse all elevate Δ FosB in the dorsal (caudate–putamen) and ventral striatum (Atkins et al., 1999; Perrotti et al., 2004, 2008). In the ventral striatum (i.e., nucleus accumbens), however, each of these factors differentially elevates Δ FosB in specific cell types. For example, chronic stress elevates Δ FosB in the dynorphin +/ substance P+ and enkephalin+ subsets of medium spiny dopamine neurons in the ventral striatum (Perrotti et al., 2004). Antipsychotic drugs elevate Δ FosB in the enkephalin+ dopamine neurons in the ventral striatum (Atkins et al., 1999; Hiroi & Graybiel, 1996), and drugs of abuse elevate Δ FosB in the dynorphin+/substance P+ dopamine neurons in the ventral striatum (Moratalla, Elibol, Vallejo, & Graybiel, 1996; Nye, Hope, Kelz, Iadarola, & Nestler, 1995; Perrotti et al., 2008). It is this latter pattern of Δ FosB expression in the dorsal striatum and in the dynorphin+/substance P+ dopamine neurons in the nucleus accumbens that we refer to as “striatal” expression in this article (unless otherwise noted) because it is this pattern of expression that is most relevant to natural rewards, drugs of abuse, and addiction (Colby, Whisler, Steffen, Nestler, & Self, 2003; McClung et al., 2004; Olausson et al., 2006; Werme et al., 2002), and it is this pattern of expression found in the transgenic mice used in our studies (Kelz et al., 1999).

Interestingly, the elevation of Δ FosB by drugs of abuse requires chronic rather than acute exposure (McClung et al., 2004; Nye et al., 1995; Nye & Nestler, 1996). Thus, although acute exposure to drugs rapidly increases many Fos family proteins in the striatum, such as c-Fos and FosB (Daunais & McGinty, 1994; B. Hope, Kosofsky, Hyman, & Nestler, 1992; Persico, Schindler, O’Hara, Brannock, & Uhl, 1993; Sheng & Greenberg, 1990), there is only a very small increase in Δ FosB (Nestler, 2001a; Nestler et al., 1999). However, once generated, Δ FosB is relatively stable and has an in vivo half-life of more than 1 week compared with 10–12 hr for other Fos proteins (Chen et al., 1997). This stability allows for the slow accumulation of Δ FosB with chronic exposure to drug. Other Fos proteins, in comparison, demonstrate a desensitized response over time (Hope et al., 1992, 1994; Moratalla et al., 1996; Nye et al., 1995). Chronic drug exposure, then, allows Δ FosB to reach levels at which it can affect gene expression and become behaviorally relevant.

There is a growing body of literature demonstrating that elevation of Δ FosB increases the perceived reward value of drugs of abuse. For example, preference for drug-associated locations, modeled by conditioned place preference, is increased in mice with elevated Δ FosB in the striatum (Kelz et al., 1999). Acquisition and maintenance of drug-taking behavior, as well as motivation to get drug, are similarly increased in mice with elevated Δ FosB (Colby et al., 2003). Although progress has been made in understanding the effects of Δ FosB in numerous aspects of drug addiction, one area that has not been investigated is the effect of Δ FosB on drug-induced devaluation of natural rewards. In humans, this phenomenon is manifested in reduced motivation for work, friends, family, and monetary gain (e.g., Goldstein et al., 2006, 2008; Jones, Casswell, & Zhang, 1995; Nair et al., 1997; Santolaria-Fernandez et al., 1995).

Our data suggest that this devastating consequence of addiction in humans can be modeled in rodents using the reward comparison paradigm (Grigson & Twining, 2002). In this paradigm, access to an otherwise palatable saccharin cue is followed by access to a drug of abuse, such as morphine or cocaine. Under these circumstances, rats and mice come to avoid intake of the taste cue in anticipation of the administration of the drug (Grigson, 1997; Grigson & Twining, 2002; Risinger & Boyce, 2002). According to the reward comparison hypothesis, intake of a

natural reward cue is avoided after pairings with a drug of abuse, at least initially (see Wheeler et al., 2008), because the value of the gustatory stimulus pales in comparison to the potent rewarding properties of the drug (Grigson, 1997). This view differs from the long-standing conditioned taste aversion (CTA) account of the data—that is, the view differs from the suggestion that rats avoid intake of the taste cue because it predicts aversive drug properties (Nachman, Lester, & Le Magnen, 1970; Riley & Tuck, 1985).

If the reward comparison hypothesis is correct, any condition or circumstance that augments the perceived value of the drug reward should augment avoidance of the lesser saccharin cue. In accordance, drug-sensitive Lewis rats exhibit greater avoidance of a saccharin cue after saccharin–cocaine pairings than do less sensitive Fischer rats (Grigson & Freet, 2000). Sprague–Dawley rats also exhibit greater avoidance of a taste cue paired with cocaine or sucrose after a history of chronic morphine treatment (Grigson, Wheeler, Wheeler, & Ballard, 2001). Interestingly, both drug-naïve Lewis rats and Sprague–Dawley rats with a history of chronic morphine treatment have elevated Δ FosB in the nucleus accumbens (Haile, Hiroi, Nestler, & Kosten, 2001; Nye & Nestler, 1996). Experiment 1 more directly examines the role of Δ FosB in drug-induced suppression of conditioned stimulus (CS) intake by evaluating cocaine-induced suppression of intake of a saccharin cue in mice that overexpress this transcription factor in the striatum.

Experiment 1

Previous studies have demonstrated that mice suppress intake of a taste cue when paired with a drug of abuse in a manner similar to that seen in rats (Risinger & Boyce, 2002; Schroy, 2006). Much like the studies involving rats, these studies used restricted access to water and a preferred 0.15% saccharin solution as the CS (Bachmanov, Tordoff, & Beauchamp, 2001; Tordoff & Bachmanov, 2003). In these experiments, intake of a saccharin cue was suppressed when access to the saccharin was followed by the injection of 10 mg/kg cocaine (in DBA/2 mice) or 20 mg/kg cocaine (in DBA/2 and C57BL/6 mice) cocaine (Risinger & Boyce, 2002; Schroy, 2006). Therefore, Experiment 1 evaluated the suppression of intake of a 0.15% saccharin cue when paired with saline, 10 mg/kg cocaine, or 20 mg/kg cocaine in water-deprived NSE-tTA $\times$ TetOp- Δ FosB Line A mice. These adult transgenic mice (SJL $\times$ C57BL/6 background) demonstrate selective overexpression of Δ FosB in the striatum on removal of doxycycline from the water (Chen et al., 1998). On the basis of the data obtained in rats, we hypothesized that elevation of Δ FosB in these mice would augment the rewarding effects of the drug and thereby facilitate drug-induced suppression of intake of the saccharin cue relative to Δ FosB normal controls.

Method

Subjects—The subjects were 60 male NSE-tTA $\times$ TetOp- Δ FosB Line A bitransgenic mice. The mice were generated by the animal facility at the University of Texas Southwestern Medical Center in Dallas, Texas, and maintained on 100 μ g doxycycline/ml in the drinking water. This approach maintains full repression of transgenic Δ FosB expression and thereby allows for normal development (as described in Chen et al., 1998). The mice were then shipped to the animal facility at the Pennsylvania State University College of Medicine in Hershey, Pennsylvania, and quarantined for 2 months (all mice were maintained on doxycycline during transport and during quarantine). On release from quarantine, half of the mice ($n = 30$) had doxycycline removed, and Δ FosB overexpression was allowed to proceed for 8 weeks before testing, the time required for maximal Δ FosB action (McClung & Nestler, 2003). The rest of the mice ($n = 30$) remained on doxycycline for the duration of the studies. Mice weighed between 31.2 g and 45.0 g at the beginning of the experiment and were housed individually in standard, clear plastic pan cages in a temperature-controlled (21°C) animal care facility with a 12-hr light–dark cycle (lights on at 7:00 a.m.). All experimental manipulations were

conducted 2 hr (9:00 a.m.) and 7 hr (2:00 p.m.) into the light phase of the cycle. The mice were maintained with free access to dry Harlan Teklad rodent diet (W) 8604 and water, except where otherwise noted.

Apparatus—All experimental manipulations were conducted in the home cages. Modified Mohr graduated pipettes were used to provide dH₂O and saccharin access. Pipettes were converted to glass cylinders by removing the tapered ends. A rubber stopper with a stainless steel spout inserted through the center was then placed in the bottom of the cylinder, and a similar rubber stopper (minus the spout) sealed the top of the cylinder. Intake of dH₂O and saccharin was recorded in 1/10 ml.

Procedure—All subjects were weighed once a day throughout the study. After release from quarantine, and as described, the Δ FosB overexpression mice ($n = 30$) were taken off of 100 μ g/ml doxycycline. These mice received unadulterated dH₂O for the remainder of the study, and the other half of the mice ($n = 30$), the Δ FosB normal groups, continued on doxycycline. After 8 weeks of Δ FosB overexpression, baseline water intake was evaluated. For baseline measurements, all mice were placed on a water deprivation schedule that consisted of access to dH₂O (with or without doxycycline depending on the treatment group) for 1 hr beginning at 9:00 a.m. and for 2 hr beginning at 2:00 p.m. Baseline intake and body weight were recorded for 1 week. During testing, all mice received 1 hr access to 0.15% saccharin in the morning followed immediately by an intraperitoneal injection of saline ($n = 10/\text{cell}$), 10 mg/kg cocaine ($n = 10/\text{cell}$), or 20 mg/kg cocaine ($n = 10/\text{cell}$). Taste–drug pairings occurred every 48 hr for five trials. To maintain hydration, all subjects received 2 hr access to dH₂O or 100 μ g/ml doxycycline each afternoon and 1 hr access to dH₂O or 100 μ g/ml doxycycline each morning between conditioning trials, as specified by group assignment. Saccharin was obtained from the Sigma Chemical Company, St. Louis, MO, and cocaine HCl was provided by the National Institute on Drug Abuse. The saccharin solution was presented at room temperature.

Results and Discussion

CS intake—Intake and body weight were analyzed using $2 \times 3 \times 5$ mixed factorial analyses of variances (ANOVAs) varying treatment (normal vs. overexpression of Δ FosB), drug (saline, 10 mg/kg cocaine, or 20 mg/kg cocaine), and trials (1–5). Post hoc tests were conducted, where appropriate, using Neuman-Keuls tests with an alpha of .05. Observation of Figure 1 shows that overexpression of Δ FosB in the striatum is associated with a reduction rather than an augmentation of cocaine-induced suppression of intake of the saccharin cue.

Support for this observation was provided by post hoc analysis of a significant Treatment $\times$ Drug $\times$ Trials interaction, $F(8, 212) = 2.08, p < .04$. Specifically, the results of post hoc Newman–Keuls tests showed that although the 10 mg/kg dose of cocaine was ineffective in reducing CS intake in both treatment groups ($p > .05$), the 20 mg/kg dose was less effective in mice with elevated expression of Δ FosB (see Figure 1, right panel). That is, although treatment with the 20 mg/kg dose of cocaine significantly reduced intake of the saccharin cue relative to each group's saline treated controls on Trials 2–5 ($ps < .05$), mice with elevated expression of Δ FosB consumed significantly more of the saccharin cue that was paired with the 20 mg/kg cocaine than did the normal expressing controls. This pattern of behavior was significant on Trials 3–5 ($ps < .05$).

Body weight—Neither overexpression of Δ FosB in the striatum nor drug exposure significantly altered body weight. This conclusion was supported by a nonsignificant main effect of treatment, $F < 1$, or drug, $F(2, 53) = 1.07, p = .35$. The main effect of trials was significant, $F(5, 265) = 10.54, p < .0001$, indicating that body weight changed over successive trials. Finally, although the $2 \times 3 \times 6$ repeated measures ANOVA revealed a significant

Treatment $\times$ Drug $\times$ Trials interaction, $F(10, 265) = 4.35$, $p < .01$, the results of the post hoc tests were unremarkable.

Morning water intake—Morning intake of dH₂O (ml/h) on the days between conditioning trials (baseline, Trials W1-W4) is presented in Figure 2 (top left and right panels).

A $2 \times 3 \times 5$ mixed factorial ANOVA revealed that neither overexpression of Δ FosB in the striatum nor drug exposure significantly altered morning dH₂O intake as indicated by a nonsignificant Treatment $\times$ Drug $\times$ Trials interaction ($F < 1$). In addition, neither the main effect of treatment, $F < 1$, or drug, $F(2, 53) = 2.55$, $p = .09$, nor the Treatment $\times$ Drug interaction, $F(8, 212) = 1.57$, $p = .14$, was statistically significant.

Afternoon water intake—Intake of dH₂O for the 2-hr access period in the afternoon for all trials is presented in Figure 2 (bottom left and right panels). The main effect of treatment was not significant ($F < 1$), suggesting that overexpression of Δ FosB did not affect afternoon dH₂O intake overall. The main effect of drug, however, did attain statistical significance, $F(2, 53) = 7.95$, $p < .001$, as did the Treatment $\times$ Drug $\times$ Trials interaction, $F(18, 477) = 2.12$, $p < .005$. Post hoc tests of this three-way ANOVA revealed that afternoon dH₂O intake in the 10 mg/kg cocaine groups did not significantly differ from that of the saline controls ($ps > .05$). However, afternoon dH₂O intake was significantly increased in the 20 mg/kg groups compared with their saline controls, and this effect was significant on conditioning trials in which mice had avoided intake the saccharin cue in the morning (i.e., Trials 3, 4, and 5 in mice with normal Δ FosB and Trials 4 and 5 in mice with elevated Δ FosB, $ps < .05$).

Experiment 2

The results obtained in Experiment 1 are opposite those predicted on the basis of previously published data. Mice with elevated expression of Δ FosB exhibited lesser, rather than greater, avoidance of a saccharin cue following repeated saccharin–cocaine pairings. There are a number of possible explanations for these data. The most obvious, given the literature, is that this paradigm is sensitive to aversive, rather than rewarding, drug properties (Nachman et al., 1970; Riley Tuck, 1985). Elevated Δ FosB, then, may not only increase responsiveness to rewarding drug properties, but may decrease responsiveness to aversive drug properties as well. If this is the case, then mice with elevated Δ FosB may also be expected demonstrate smaller LiCl-induced CTAs than mice with normal expression of Δ FosB. To test this hypothesis, the same mice were run in a standard conditioned taste aversion paradigm which they received 1 hr access to a novel 0.1 M NaCl solution and, immediately thereafter, were injected intraperitoneally with saline, 0.018 M LiCl, or 0.036 M LiCl.

Method

Subjects—The subjects were 58 (29 overexpressed Δ FosB and 29 normal Δ FosB) male NSE-tTA $\times$ TetOp- Δ FosB Line A mice used in Experiment 1. Mice were counterbalanced to evenly distribute prior saccharin–saline or saccharin–cocaine experience among the groups. At the time of testing, mice in the experimental group had overexpression of Δ FosB in the striatum for approximately 17 weeks, and all mice weighed between 31.7 and 50.2 at the beginning of the experiment. They were housed individually and maintained as described above.

Apparatus—The apparatus was the same as that described Experiment 1.

Procedure—All subjects were weighed once a day throughout the study. For baseline measurements, all mice were placed on the water deprivation schedule described above (1 hr a.m. and 2 p.m.), with or without doxycycline as per group assignment. Base line intake and body weight were recorded for 1 week. During testing, all mice received 1 hr access to 0.1 M

NaCl in the morning followed immediately by an intraperitoneal injection of saline ($n = 9/\text{cell}$), 0.018 M LiCl ($n = 10/\text{cell}$), or 0.036 M LiCl ($n = 10/\text{cell}$). In rats, the suppressive effect of a 0.009 M dose of LiCl has been matched to that of 10 mg/kg dose of cocaine (Grigson, 1997). However, given the prior experience of the mice in Experiment 1 and evidence showing that such prior experience can retard the development and/or expression of a subsequent CS–unconditioned stimulus (US) association (Twining et al., 2005), we used slightly higher doses of LiCl (0.018 M and 0.036 M). Taste–drug pairings occurred every 48 hr for five trials. All subjects received 2 hr access to dH₂O or 100 µg/ml doxycycline each afternoon and 1 hr access to dH₂O or 100 µg/ml doxycycline each morning between conditioning trials. NaCl was obtained from Fisher Chemical, Pittsburgh, PA; LiCl was obtained from the Sigma Chemical Company, St. Louis, MO. The NaCl solution was presented at room temperature.

Results and Discussion

CS intake—Intake was analyzed using a $2 \times 3 \times 5$ mixed factorial ANOVA varying treatment (normal vs. overexpression of ΔFosB), drug (saline, 0.018 M LiCl, or 0.036 M LiCl), and trials (1–5). Post hoc tests were conducted, where appropriate, using Neuman–Keuls tests with an alpha of .05. The effect of overexpression of ΔFosB on LiCl CTA learning is shown in Figure 3.

The results of the ANOVA revealed a significant Drug $\times$ Trials interaction, $F(8, 204) = 5.08$, $p < .001$, showing that all mice, regardless of ΔFosB expression, avoided intake of the NaCl CS that had been paired with the illness-inducing agent LiCl relative to the saline-treated subjects. Unlike the cocaine data described above, the three-way ANOVA did not approach statistical significance ($F < 1$). In addition, there was no significant effect of treatment (i.e., doxy or water; $F < 1$), Treatment $\times$ Trial interaction ($F < 1$), or Treatment $\times$ Drug interaction ($F < 1$). Even so, observation of the data shown in Figure 3 suggests that the suppressive effect of LiCl, like that of cocaine, may have been smaller in the overexpressing ΔFosB mice. Thus, we reanalyzed the treatment groups separately using 3×5 mixed factorial ANOVAs varying drug and trials. The results of these ANOVAs confirmed a significant Drug $\times$ Trials interaction for both the normal, $F(8, 100) = 3.48$, $p < .001$, and the overexpressed, $F(8, 108) = 2.19$, $p < .033$, ΔFosB mice. Post hoc tests showed a significant reduction in CS intake by the higher dose of LiCl on Trials 3–5 for the normal mice and on Trials 3 and 4 for the overexpressing mice ($ps < .05$).

Despite a relatively high sample size, the LiCl data are more variable than were the cocaine data in Experiment 1. The variability shown in Figure 3 likely relates to the history of saline or cocaine treatment in Experiment 1. In an effort to test this hypothesis, we reanalyzed the LiCl CTA data using a $2 \times 2 \times 3 \times 5$ mixed factorial ANOVA varying history (saline vs. cocaine), treatment (normal vs. overexpression of ΔFosB), drug (saline, 0.018 M LiCl, or 0.036 M LiCl), and trials (1–5). For the sake of simplicity, cocaine history reflected an average of the data from mice with a history of experience with the 10 mg/kg and the 20 mg/kg dose cocaine. Similar to the results of the initial analysis, the four-way interaction also failed to attain statistical significance, $F(8, 180) = 1.34$, $p = .22$. A history of saccharin–saline or saccharin–cocaine pairings, then, likely contributes to variability in the data, but the impact is not uniform, and inclusion of the history factor is not helpful in revealing statistically significant differences in the magnitude of the LiCl-induced CTA between the normal ΔFosB mice and the mice with an overexpression of ΔFosB . In sum, LiCl suppresses intake of the NaCl CS, and although there is a tendency for a slightly diminished effect in the overexpressing ΔFosB mice, the difference between treatment groups did not approach statistical significance.

Taken together, the results from Experiments 1 and 2 show that mice with elevated ΔFosB consume significantly more of a saccharin CS after saccharin–cocaine pairings and tend to consume more of a NaCl CS after NaCl–LiCl pairings. The tendency to consume more of the

drug-associated CSs (particularly in Experiment 1) may be the result of an increase in sensitivity to the rewarding properties of the saccharin and/or the NaCl CS because elevated levels of Δ FosB are known to be associated with an increase in responsiveness to other natural rewards such as food pellets (Olausson et al., 2006) and wheel running (Werme et al. 2002). Experiment 3 tests whether these mice with elevated striatal levels of Δ FosB respond more greatly to the rewarding properties of a range of concentrations of sucrose and salt in two-bottle intake tests with water.

Experiment 3

Experiment 3 was designed to examine the hypothesis that the reduced suppression of CS intake by the overexpressing Δ FosB mice in Experiment 1 was a result of augmentation of the perceived reward value of not only the drug of abuse, but the natural saccharin reward cue as well. To evaluate this hypothesis, we used one- and two-bottle intake tests to examine the effect of overexpression of Δ FosB on intake of a rewarding (sucrose) stimulus. In addition, given the tendency for these mice to overconsume the NaCl CS after NaCl–LiCl pairings in Experiment 2, we also used one- and two-bottle intake tests to examine the effect of elevated Δ FosB on intake of a range of concentrations of the more “neutral” NaCl solutions. Three concentrations of NaCl (0.03 M, 0.1 M, and 0.3 M) and sucrose (0.01 M, 0.1 M, and 1.0 M) were examined. It was hypothesized that if elevation of Δ FosB augments the rewarding value of natural rewards, intake of sucrose should be greater in the experimental mice as compared with controls.

Method

Subjects—The subjects were 28 (14 overexpressed Δ FosB and 14 normal Δ FosB) male NSE-tTA $\times$ TetOp- Δ FosB Line A mice used in Experiment 1. At the time of testing, mice in the experimental group had overexpression of Δ FosB in the striatum for approximately 25 weeks. In addition, mice had prior experience with saccharin–sucrose pairings in an unsuccessful anticipatory contrast experiment (the parameters that support anticipatory contrast in mice are still under investigation). Mice weighed between 31.5 and 54.5 g at the beginning of the experiment. They were housed and maintained as previously described.

Apparatus—The apparatus was the same as that described in Experiment 1.

Procedure—All subjects were weighed once daily. Over 4-day habituation period, each mouse received 1 hr access to dH₂O in the morning and 2 hr access in the afternoon. Throughout the experiment, mice with elevated Δ FosB ($n = 14$) received dH₂O to rehydrate each afternoon, and mice with normal Δ FosB ($n = 14$) received 100 μ g/ml doxycycline. Three concentrations of NaCl (0.03 M, 0.1 M, and 0.3 M) and sucrose (0.01 M, 0.1 M, and 1.0 M) were used as the tastants. Each concentration was presented to the mice during the morning 1-hr period for 3 consecutive days. The first 2 days were one-bottle presentations of the tastant and the 3rd day consisted of a two-bottle presentation of the tastant and dH₂O. The position of the bottles was counterbalanced, left and right, within groups and across two-bottle test sessions. The solutions were presented in an ascending order, and intake of NaCl was tested before sucrose. Two dH₂O-only trials were conducted between NaCl and sucrose testing. Intake was measured on each day to the nearest 1/10 ml.

Data analysis—The data were analyzed using t tests with an alpha of .05.

Results and Discussion

The data from the two-bottle tests were most informative and, thus, are presented here (see Figure 4). Baseline one-bottle water intake is also shown as a point of reference.

NaCl preference—Overall, the history of CTA learning to the 0.1 M NaCl solution after pairings with the relatively low doses of LiCl did not prevent the expression of preference–aversion functions to increasing concentrations of NaCl when examined in the intake test. In mice with normal Δ FosB (top left panel), intake of the two lowest concentrations of NaCl (0.03 M and 0.1 M) did not differ from intake of dH₂O in the two-bottle tests ($ps > .05$). The highest concentration of NaCl (0.3 M), however, was significantly less preferred than dH₂O ($p < .0001$), consistent with the aversive nature of this concentration (Bachmanov, Beauchamp, & Tordoff, 2002). In the mice with elevated Δ FosB (top right panel), a similar pattern was evident with the 0.3 M concentration of NaCl ($p < .01$), indicating that elevation of Δ FosB did not significantly alter the response to this aversive stimulus. A different pattern, however, occurred with the lower concentrations of NaCl. Specifically, rats with elevated expression of Δ FosB demonstrated a preference for the lower 0.03 M and 0.1 M concentrations of NaCl relative to dH₂O in the two-bottle tests ($ps < .03$). Elevation of Δ FosB, then, may shift the preference for lower concentrations of NaCl from neutral to preferred.

Sucrose preference—Analyses using t tests for dependent samples indicated that in mice with normal Δ FosB, intake of the lowest concentration of sucrose (0.01 M) was not significantly different than dH₂O ($p = .82$). In contrast, the 0.1 M and 1.0 M sucrose concentrations were significantly preferred to dH₂O ($ps < .0001$). In the mice with elevated Δ FosB, sucrose was significantly preferred to dH₂O across all concentrations tested ($ps < .02$). This finding provides support for the conclusion that elevation of Δ FosB increases the preference for natural rewards.

General Discussion

The data in this article demonstrate that elevation of Δ FosB in the striatum is associated with attenuated cocaine-induced suppression of saccharin intake. This finding runs counter to our original prediction that such elevations should facilitate the suppressive effects of cocaine. Specifically, elevation of Δ FosB increases the rewarding value of drugs of abuse (Colby et al., 2003; Kelz et al. 1999), and animals with an addiction-prone phenotype or with history of treatment with chronic morphine (both of which produce elevations of Δ FosB) demonstrate greater drug-induced suppression of saccharin intake relative to controls (Grigson & Freet, 2000; Grigson et al., 2001). It is important to note, however, that subjects in the previous experiments possessed not only elevated Δ FosB, but also the myriad neuronal adaptations that result from exposure to drugs of abuse or the addiction-prone phenotype (Nestler, 1995, 2001b; Nestler & Aghajanian, 1997). These additional adaptations undoubtedly contributed to behavior and present a possible confound when attempting to interpret the role of Δ FosB, *per se*, in drug-induced suppression of CS intake. This confound was controlled for in these experiments (i.e., all subjects were the same with the exception of elevations in Δ FosB), allowing for a more direct interpretation of the role of Δ FosB in the phenomenon. As stated above, the current data demonstrate that cocaine-induced suppression of saccharin intake occurs in the presence of elevated striatal Δ FosB, but the effect is attenuated relative to controls. Elevation of Δ FosB in the striatum, then, serves to reduce rather than enhance cocaine-induced suppression of saccharin intake.

There are several interpretations of the attenuated effect that can be excluded fairly quickly. First, it is possible that elevations in Δ FosB decreased the rewarding value of cocaine. This seems an unlikely explanation given the extensive literature linking elevated Δ FosB to an increase in the perceived reward value of cocaine and other drugs of abuse (Colby et al., 2003; Kelz et al., 1999; McClung & Nestler, 2003; McClung et al., 2004; Nestler et al., 2001, 1999). Second, the attenuation may reflect species differences in drug-induced suppression and the behavioral effects of Δ FosB. Again, the literature does not support this possibility because rats and mice demonstrate similar trends in drug-induced suppression of

CS intake (Grigson, 1997; Grigson & Twining, 2002; Risinger & Boyce, 2002) and behavioral sensitization by Δ FosB (Kelz et al., 1999; Olausson et al., 2006; Werme et al., 2002; Zachariou et al., 2006). Finally, it is possible that elevation of Δ FosB may create a general associative deficit that would attenuate cocaine-induced suppression of saccharin intake. This possibility, too, appears unlikely because disruptions of this nature are not seen in the learning or performance of operant behavior (Colby et al., 2003), and acquisition of the LiCl-induced CTA did not differ, significantly, as a function of Δ FosB expression in Experiment 2. The Δ FosB overexpressing mice also behave normally in the Morris water maze and in conditioned place preference (Kelz et al., 1999).

Another possibility is raised by a traditional CTA interpretation of the data in Experiment 1. That is, if cocaine-induced suppression of intake of the saccharin cue were driven by aversive drug properties, then one would conclude that elevated Δ FosB reduced, at least in part, the impact of these aversive drug properties. In fact, there is evidence that drugs of abuse have aversive properties. Cocaine has been shown to potentiate panic like flight responses (Blanchard, Kaawaloa, Hebert, & Blanchard, 1999) and defensive behaviors (Blanchard & Blanchard, 1999) in mice. Even so, most evidence has suggested that drugs of abuse suppress CS intake via rewarding drug properties (Grigson & Twining, 2002; Grigson, Twining, Freet, Wheeler, & Geddes, 2008). For example, lesions of the gustatory thalamus (Grigson, Lyuboslavsky, & Tanase, 2000; Reilly & Pritchard, 1996; Scalera, Grigson, & Norgren, 1997; Schroy et al., 2005), gustatory thalamocortical loop (Geddes, Han, & Grigson, 2007), and insular cortex (Geddes, Han, Baldwin, Norgren, & Grigson, 2008; Mackey, Keller, & van der Kooy, 1986) disrupt suppression of a saccharin cue by sucrose and drugs of abuse, but not by LiCl. Similarly, selective rat strains demonstrate differential suppression for a drug of abuse or sucrose US, but not for a LiCl US (Glowa, Shaw, & Riley, 1994; Grigson & Freet, 2000). Similar dissociations have been demonstrated with manipulations of deprivation state (Grigson, Lyuboslavsky, Tanase, & Wheeler, 1999) and in rats with a chronic morphine history (Grigson et al., 2001). In addition, in Experiments 3 and 2, the elevation of Δ FosB had no effect on either the unconditioned or the conditioned response to aversive stimuli, respectively. Thus, relative to the normal mice, mice with elevated Δ FosB exhibited a similar aversion to the potent 0.3 M NaCl solution in Experiment 3 and a statistically similar aversion to the LiCl-associated CS in Experiment 2.

This evidence aside, in a recent study we obtained evidence that cocaine-induced suppression of intake of a saccharin cue is associated with the onset of a conditioned aversive state (Wheeler et al., 2008). We hypothesize that the aversive state is mediated, in large part, by the development of cue-induced withdrawal (Grigson et al., 2008; Wheeler et al., 2008). The possibility, then, might be considered that the increase in Δ FosB in the striatum leads to less avoidance of the drug-associated cue because the drug supports the development of less cue-induced withdrawal. Although possible, this conclusion also seems difficult to accept because in rats, more aversion to the CS (as measured by an increase in aversive taste reactivity behavior) is associated with an increase in responsiveness to the drug (Wheeler et al., 2008). Thus, using this logic, we would be forced to conclude that mice with elevated Δ FosB are more responsive to the rewarding properties of the drug, as has been shown, but also exhibit less cue-induced craving or withdrawal. This seems unlikely.

A more heuristic explanation for the attenuated effect in the current data is that although elevation of Δ FosB increased the rewarding effects of cocaine in these mice, it also increased the perceived rewarding value of saccharin. If Δ FosB increased the absolute reward value of saccharin and cocaine similarly, the perceived increase in the reward value of saccharin would be greater (compared with cocaine) as stated by Weber's law (i.e. sensitivity to a perceived change inversely depends on the absolute strength of the stimuli; Weber, 1846). Such an increase in relative CS palatability would decrease the relative difference between the rewards and

attenuate the reward comparison effect (Flaherty Rowan, 1986; Flaherty, Turovsky, & Krauss, 1994). This interpretation is further supported by the literature showing that elevation of Δ FosB increases responding for natural rewards. For example, wheel running (Werme et al., 2002) and motivation for food pellets (Olausson et al., 2006) are both increased with elevation of Δ FosB. In addition, the data obtained in Experiment 3 also demonstrate that elevation of Δ FosB increases preference for sucrose (0.03 M, 0.1 M, and 0.3 M) and for lower concentrations of NaCl (0.01 and 0.1 M) in two-bottle tests with water.

The goal of this experiment was to evaluate the effect of elevated Δ FosB in the reward comparison paradigm, a procedure that thought to model drug-induced devaluation of natural rewards human addicts (Grigson, 1997, 2000, 2002; Grigson & Twining, 2002; Grigson et al., 2008). Addiction has a complex behavioral phenotype, and many factors are involved in the behavioral expression of addiction. However, on the basis of the current literature, the elevation of Δ FosB induced by chronic exposure to drugs of abuse appears to play a role in the sensitization of the rewarding effects the drug (Colby et al., 2003; Kelz et al., 1999) and in increased responding for natural rewards (Olausson et al., 2006; Werme et al. 2002). This article sheds light on the effect of Δ FosB in the interaction of these rewards. The elevation of Δ FosB does not appear necessary for drug-induced devaluation of the saccharin cue. In fact, control mice suppressed intake of the saccharin cue appropriately. Rather, our data suggest that the elevation of Δ FosB in striatum may oppose this phenomenon by reducing the perceived difference in reward value between natural rewards and drugs of abuse. In so doing, mice with this phenotype may actually be better protected from drug when it presented with viable natural rewards. In support, access to saccharin blunts the nucleus accumbens dopamine response to the initial injection of morphine in Sprague–Dawley rats (Grigson & Hajnal, 2007) and brief daily access to a palatable sucrose solution decreases rats' willingness to work for cocaine early in acquisition (Twining, 2007) Thus, although the elevation of Δ FosB may predispose rats and mice to drug-taking behavior in the absence of alternative rewards, it may protect the subject from drug-taking behavior in the presence of a viable alternative natural reward.

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Reward Comparison in NSE-tTA x TetOp-deltaFosB Line A mice

Figure 1.

Mean ($\pm$ SEM) intake (ml/1 hr) of 0.15% saccharin following five pairings with the intraperitoneal injection of saline, 10 mg/kg cocaine, or 20 mg/kg cocaine in NSE-tTA $\times$ TetOp- Δ FosB Line A mice with normal (left panel) or elevated (right panel) levels of Δ FosB in the striatum. An asterisk denotes significant difference from saline controls. A plus sign denotes significant difference across treatment groups within the same drug group.

Reward Comparison in NSE-tTA x TetOp-deltaFosB Line A mice

Figure 2.

Mean ($\pm$ SEM) intake of dH₂O in the morning (ml/1 hr; top panels) and afternoon (ml/2 hr; bottom panels) in NSE-tTA $\times$ TetOp- Δ FosB Line A mice with normal (left panels) or elevated (right panels) levels of Δ FosB in the striatum as a function of drug group (saline, 10 mg/kg cocaine, or 20 mg/kg cocaine) and trials. An asterisk denotes significant difference from saline controls. B = baseline trial, W = water only trial.

Figure 3.

Mean ($\pm$ SEM) intake (ml/1 hr) of 0.1 M NaCl after five pairings with the intraperitoneal injection of saline, 0.018 M LiCl, or 0.036 M LiCl in NSE-tTA $\times$ TetOp- Δ FosB Line A mice with normal (left panel) or elevated (right panel) levels of Δ FosB in the striatum.

Figure 4.

Mean ($\pm$ SEM) intake (ml/1 hr) of a range of concentrations of NaCl (top panels) and sucrose (bottom panels) versus dH₂O in NSE-tTA $\times$ TetOp- Δ FosB Line A mice with normal (left panels) or elevated (right panels) levels of Δ FosB in the striatum. An asterisk denotes significant difference from dH₂O intake.