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REVIEW ARTICLE

Molecular neurobiology of addiction: what's all the (Δ)FosB about?

James K. Ruffle, BSc

Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Abstract

The transcription factor ΔFosB is upregulated in numerous brain regions following repeated drug exposure. This induction is likely to, at least in part, be responsible for the mechanisms underlying addiction, a disorder in which the regulation of gene expression is thought to be essential. In this review, we describe and discuss the proposed role of ΔFosB as well as the implications of recent findings. The expression of ΔFosB displays variability dependent on the administered substance, showing region-specificity for different drug stimuli. This transcription factor is understood to act via interaction with Jun family proteins and the formation of activator protein-1 (AP-1) complexes. Once AP-1 complexes are formed, a multitude of molecular pathways are initiated, causing genetic, molecular and structural alterations. Many of these molecular changes identified are now directly linked to the physiological and behavioral changes observed following chronic drug exposure. In addition, ΔFosB induction is being considered as a biomarker for the evaluation of potential therapeutic interventions for addiction.

Keywords

Addiction, biomarker, DeltaFosB, epigenetics, transcription, treatment

History

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Introduction

Defining addiction

Substance dependence is defined by the American Psychiatric Association as a maladaptive pattern of substance use that subsequently leads to clinical impairment or distress (1). It is classified by the appearance of specific manifestations, where three or more occurring within 12 months support diagnosis. These are: increased substance tolerance, withdrawal, increased intake, recurrent desire to reduce substance use, frequent drug-seeking behaviors, reduction in social, occupational or recreational activities, and continual substance use despite deleterious physical or psychological consequences (1).

Addiction pathways and the nucleus accumbens

The nucleus accumbens (NAc) is the subcortical region most implicated in drug addiction. Located in the ventral striatum, it is implicated in many emotional constructs, including pleasure (or reward) (2), addiction (3), and more recently fear (4), the placebo effect (5) and aggression (6). The principal cell type is represented by inhibitory medium spiny neurons (7), which synthesize and release γ-aminobutyric acid (GABA) (8).

The fundamental neuronal circuit underlying reward is well understood. The critical input to the NAc is from the ventral tegmental area (VTA) – the mesolimbic (dopaminergic) pathway. The VTA also sends dopaminergic signals to the caudate-putamen, olfactory tubercle, amygdala and prefrontal cortex (PFC). Following repeated drug exposure, it is understood that addiction develops through this mesolimbic pathway.

Transcription factors in addiction

The genesis of addiction and the accompanying behavioral abnormalities are thought to be closely linked to the regulation of gene expression (9). This hypothesis has been explored for more than 20 years, with evidence of genetic changes following both acute and chronic drug exposure (10–12). These genetic changes have been linked to altered levels of transcription factors.

Transcription factors are proteins that bind to DNA promoter elements, subsequently regulating the expression of the associated gene. Important factors implicated in addiction include cAMP-responsive-element-binding protein (CREB) (13), activating transcription factors (ATFs) (14), nucleus accumbens 1 (NAC-1) (15), inducible cAMP early repressors (16), early growth response (EGR) proteins (17), and delta FBJ murine osteosarcoma viral oncogene homolog B (ΔFosB) (18). This review will discuss and evaluate the

Address correspondence to James K. Ruffle, BSc, Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK, Tel: +44 077927 96965. E-mail: j.ruffle@smd10.qmul.ac.uk

evidence supporting the role of ΔFosB in chronic drug exposure, and recent therapeutic opportunities linked to this.

ΔFosB

FosB is a transcription factor encoded by the *FOSB* gene on human chromosome 19 (19q13.32). Fos refers to a gene family consisting of four main members: Fos, FosB, FosL1 and FosL2 (18,19). These Fos family transcription factors heterodimerise with Jun family proteins, namely JunD (20), JunB (21) and, to a lesser extent, c-Jun (11). The heterodimers form activator protein-1 (AP-1) complexes, which bind to AP-1 sites on promoter sequences, causing gene expression or repression (22) (Figure 1).

The Δ variant is a truncated form of the FosB transcription factor with high stability, and it accumulates significantly in repeated drug exposure (21). Generated by alternative splicing of the *FOSB* gene (23), it is a 237 amino acid protein lacking the 101 amino acid FosB C terminus (18). Despite truncation, ΔFosB still dimerises with Jun proteins and forms AP-1 complexes. This pathway is linked to numerous downstream cellular and molecular changes underpinning addiction (22). The regulation of ΔFosB and the cause of its high stability are multifactorial. Well-defined mechanisms are (i) alternative splicing, and (ii) structure and post-translational modification. These are discussed herein.

Alternative splicing

ΔFosB is produced following splicing of cryptic splice sites within the last coding exon from FosB pre-mRNA transcript (24). This splicing leads to an open-reading-frame shift producing a stop codon. However, the binding of polypyrimidine tract binding protein (PTB) to a CU-rich sequence at the 3′ end of I4 causes its retention (thus PTB silences I4 splicing, conferring a regulatory role in ΔFosB mRNA production) (24–26). PTB-I4 binding is dependent upon protein kinase A-dependent phosphorylation, and splicing assembly factor U2AF^{65} additionally competes for the binding site (24,27). A further regulator of ΔFosB expression is protein kinase G, mediated by suppression of inhibitory D2 receptors (28). This is consistent with studies of Parkinson's disease, where the loss of dopaminergic neurons induces ΔFosB expression (20,29,30). Additionally, a spliced isoform (ΔFosB-2) exists, formed by in-frame deletion of exon 3 (31). However, whilst ΔFosB-2 expression has recently been demonstrated using methamphetamine in rat models (32), its influence on transcription regulation, gene expression and addiction behavior is unknown and requires investigation.

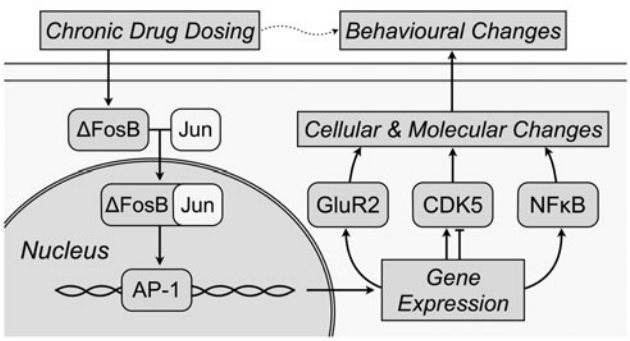

Figure 1. Cellular schematic of ΔFosB expression and its sequential molecular effects following chronic drug exposure. Following repeated drug exposure, ΔFosB is induced in numerous brain regions. Alternative splicing regulates ΔFosB expression, and structural modifications occur conferring its high stability. After expression, ΔFosB heterodimerises with Jun family proteins and translocates to the cell nucleus. Inside the nucleus, the ΔFosB:Jun heterodimer undergoes complex formation with activator protein-1 (AP-1) on DNA. Depending on the administered substance (e.g. cocaine), this allows for the expression of numerous gene targets, such as the GluR2 AMPA subunit, Cyclin dependent kinase 5 (Cdk5) and Nuclear Factor κB (NFκB). Following repeated opiate dosing, GluR2 and NFκB induction are similarly induced, whilst a decrease in Cdk5 expression occurs. The expression (or repression) of these three different targets causes sequential cellular and molecular changes which likely result in the behavioral phenotype characterizing addiction.

Structure and post-translational modification

The C terminal of non-truncated FosB contains two degron domains (23). These are sequences of amino acids that direct normal protein ubiquitination and degradation by proteasomal-dependent and independent complexes (18). The splice variant ΔFosB lacks this C-terminus, and hence does not have the degron domains. This significantly increases the protein half-life approximately four-fold due to the absence of the proteosomal-dependent degron, and an additional two-fold for the absent proteosomal-independent degron (23). Further stability is conferred upon ΔFosB by phosphorylation of serine residue Ser27 by casein kinase 2 (although additional kinases may also be involved) (33). Contrasting to the ΔFosB protein, its mRNA is relatively unstable and degrades relatively quickly (similar to other Fos family proteins) (30,34). Chen et al. show ΔFosB mRNA to peak at 30 minutes post-stimulus, returning to baseline within 12 hours (21).

The high molecular stability of ΔFosB means it is retained in neurons for several weeks after drug intake has ceased, before returning to baseline levels (35,36). However, behavioral changes seen in repeated drug exposure (such as relapse) may occur years after drug intake cessation (37). This implies that ΔFosB interacts with other molecules to be causally linked to long-term behavioral effects, given its down-regulation after several weeks. Consequently, it was proposed that ΔFosB acts as a ''molecular switch'' in the genesis and continuity of addiction (34,38).

Differential transcription factor expression in acute and chronic drug exposure

Acute drug exposure (1–2 hours post single dose) leads to induction of many transcription factors (such as c-Fos and CREB), primarily in the NAc and the dorsal striatum (3,10,39). It is thought that transcription factors induced after acute intake, but not chronically, are linked to tolerance and sensitization (21,40,41).

Significantly different transcriptional responses are seen after chronic drug exposure (repeated dosing over days). In acute dosing, induced proteins return to baseline levels within hours of the initial drug administration (due to molecular instability) (3). However, in chronic drug exposure, isoforms of ΔFosB accumulate in multiple brain regions for weeks (40–44). Drugs shown to induce ΔFosB in these regions include amphetamine (45), cocaine (30,44), ethanol (46),

methamphetamine (43), morphine (37,47), neuroleptics (48), nicotine (49) and Δ9-tetrahydrocannabinol (48).

ΔFosB is consistently induced in the NAc (3,45,46). It has also been detected in numerous other brain regions, such as the amygdala (50, 51), caudate-putamen (52), dorsal striatum (53,54), hippocampus (46), prefrontal cortex (55), ventral pallidum (42), and VTA (35,56). However, ΔFosB induction in some brain regions is not consistently reproduced, and so the exact regions of expression remain somewhat controversial (57,58). There is additionally high variability in regional ΔFosB expression depending on the administered substance (42,46). Furthermore, ΔFosB induction in brain regions is somewhat (although not universally) selective for substance P-dynorphin-containing medium spiny neurons (53,59,60).

The neuroadaptation to addiction by ΔFosB extends beyond the reward circuitry of the NAc and VTA. A study has shown ΔFosB expression to also occur in the paraventricular nucleus (PVN) of the hypothalamus after chronic cocaine exposure (61). This induction was mediated by dopamine D1 receptors, and it was subsequently suggested that ΔFosB may also have a role in the hypothalamic-pituitary axis (61). A further study has reported ΔFosB induction in the PVN and nucleus tractus solitarius as a result of morphine dependence, and it was consequently proposed that ΔFosB may additionally have a neuroadaptive role in the brain stress system (62). Recent data also show glucocorticoids to regulate ΔFosB expression following repeated opiate dosing, strengthening the link between brain stress hormones and addiction (63). It is plausible that with additional research ΔFosB will be implicated in further neural pathways.

Interestingly, forms of psychogenic chronic stress including restraint stress (51,64), social defeat (65,66), and chronic unpredictable stress (67) have also been shown to increase ΔFosB in dynorphin and enkephalin-containing medium spiny neurons (68). This is thought consequential to serum response factor (SRF) expression, as genetic deletion of SRF in the NAc was related to pro-depressant phenotypes (65). It is suggested that ΔFosB expression may encompass a stress coping response (69,70), possibly by increased brain sensitivity to neural reward pathways (71). This is consistent with research showing that ΔFosB induction is essential for a behavioral response to antidepressant fluoxetine, following social defeat (72).

Behavioral responses to ΔFosB induction

Given the observation of ΔFosB expression in multiple regions following repeated drug exposure, any consequential behavioral effects must be elucidated. The characterized influence of ΔFosB in addiction is largely from studies utilizing bitransgenic mice. Using this genetic methodology, ΔFosB can be selectively induced and overexpressed in dynorphin-containing medium spiny neurons (including brain regions such as the NAc and dorsal striatum) (73). This model is practical and its use is justified, as the selective ΔFosB overexpression occurs in regions where it is thought addictive substances similarly induce it. Viral-mediated gene transfer has also been used for ΔFosB overexpression, producing similar findings (37,74). In addition, genetic tools such as chromatin immunoprecipitation have more recently been used for investigating the epigenetic influence of ΔFosB (74,75).

It is well characterized that ΔFosB overexpression in the NAc increases reward drive and substance consumption (73,76,77), whilst decreasing aversion sensitivity (54). An opiate study supported the above (37), utilizing bitransgene methodology that has been shown to yield an ~8-fold ΔFosB expressional increase (73). Overexpression of ΔFosB in the NAc increased opioid reward sensitivity, exaggerated dependence, and potentiated tolerance to morphine analgesia (37). Zachariou et al. suggested these findings were mediated by dynorphin repression (37), considering ΔFosB selectivity for dynorphin-containing neurons (59). Given dynorphin is thought to have a repressive effect on the reward pathways between the VTA and NAc (78,79), ΔFosB could act via disinhibition to enhance reward circuitry (37,80). However, this hypothesis remains controversial, as contrasting studies have suggested ΔFosB-mediated dynorphin activation (81). Needless to say, whether ΔFosB acts via disinhibition (37) or dynorphin activation (81), it is clearly implicated in the behavioral phenotype accompanying addiction.

Studies have also shown a relationship between ΔFosB expression and self-dosing of addictive substances. For example, ΔFosB-overexpressing mice were found to exert greater effort to self-administer cocaine, and at higher doses, compared to normal controls (59). It was concluded that ΔFosB increases the incentive properties of cocaine, which likely contributes to addiction and may predispose individuals to relapse after drug cessation. Interestingly, and perhaps paradoxically, recent ΔFosB knock-out (KO) studies have shown KO subjects to exhibit increased behavioral abnormalities following nicotine and stress exposure, such as an exaggerated locomotor response (82). It was suggested ΔFosB KO has a pleiotropic effect on behavior, although further studies are required to reproduce and evaluate this finding (82).

Molecular effects of ΔFosB and consequential behavioral changes

Given the diverse behavioral alterations following ΔFosB induction, it is rational to investigate the molecular basis underpinning these changes.

Molecular cascades

Induction of ΔFosB, heterodimerisation with Jun family proteins, and AP-1 related transcription causes numerous effects. It is thought this cascade induces expression of many different genes, subsequently causing alterations to neuronal morphology and behavior (21,83). The protein kinase A (PKA) pathway may also be implicated in these changes (84). Altered gene expression includes receptors, synaptic proteins, ion channels, intracellular signaling molecules and cytoskeletal peptides (85,86).

GluR2 induction

Kelz et al. showed the behavioral effects of chronic cocaine administration (namely increased sensitivity to reward) were mediated by a specific molecular change (73).

ΔFosB induction led to an increased expression of the GluR2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) excitatory glutamate receptor (73). This expression has been confirmed by multiple cocaine studies (87,88). It is thought that opiates cause similar events (53); however, further studies must investigate a proposed relationship between opiate intake and GluR2. Upregulation of the GluR2 subunit decreases AMPA conductance (by removal of the channel calcium permeability), which is thought a mechanism for the decreased glutamatergic transmission observed in the affected neurons after repeated drug exposure (89). Moreover, it is thought that this upregulation serves as a mechanism for increased drug reward, and thus supports the emergence of addiction (73) (Table 1).

CDK5 expression

Cyclin dependent kinase 5 (Cdk5) is a protein kinase required in neuronal development, survival and synaptic signaling (90). It is also implicated in addiction (91). By use of overexpression techniques, it has been shown that ΔFosB induces Cdk5 (including its cofactor p35) in brain regions such as the NAc (92), striatum (74,93) and hippocampus (94). Additionally, upregulation of the p25 subunit may regulate the Cdk5 phosphorylation properties of specific substrates, such as Pak1 (an enzyme of the RhoGTPase pathway involved in neuronal morphological changes) (90). AP-1 binding sites within the Cdk5 promoter sequence mediate its induction (94), whilst ΔcJun inhibits it (92).

Cdk5 induction is associated with subsequent changes in the phosphorylation state of synaptic proteins (such as the GluR1 subunit) (93). Behavioral changes parallel to Cdk5 induction are also observed. One study showed that infusion of roscovitine and olomoucine (Cdk5 inhibitors) increased cocaine sensitisation, enhanced locomotor response (to a drug challenge) and increased the drug motivational effects (91).

An important structural finding in cocaine addiction is the observation of increased dendritic branching (95–97). Studies suggest this may be attributable to Cdk5 expression, where increased proximal dendritic spine density is found with repeated dosing (60,91,95). This illustrates a role for ΔFosB-mediated Cdk5 expression in neural plasticity and structural alterations. Moreover, the neuroplasticity effects of Cdk5 in the NAc were correlated with decreased drug response (91) (Table 1).

Paradoxical to cocaine studies, a decrease in Cdk5 following chronic morphine administration has been reported (98). In addition, repeated opiate dosing is shown to decrease spine density (96). Coalescing the findings of morphine decreasing Cdk5 levels and that Cdk5 increases spine density (98,99); it is possible that the reverse structural response to cocaine occurs. However, further investigations concerning Cdk5 and opiates are required.

NFκB activation

Another target of ΔFosB is the induction of nuclear factor-κB (NFκB) (100,101). NFκB is a transcription factor implicated in the expression of various parts of the inflammatory response, including cytokines and cell adhesion molecules. Chronic cocaine administration was shown to stimulate NFκB induction in the NAc and caudate-putamen (100,102). Similarly, morphine-dependent NFκB activation has been reported (although this was not investigated with regards to an association with ΔFosB) (103). Correlating induction with behavioral change, NFκB expression in the NAc is thought responsible for mediation of the positive reinforcement of the drug, whilst in the caudate-putamen being associated with changes of movement (100) (Table 1).

NFκB has also been linked to the observed dendritic branching in chronic drug exposure (albeit only with cocaine models). Dendritic expansion was correlated with an increase in the drug reward response (the opposite to studies investigating Cdk5) (102). The inverse relationship between Cdk5 and NFκB-induced spine growth with behavioral alteration in drug addiction is complex and warrants further investigation.

Psychological addiction

ΔFosB may have a role in psychological addiction. The orbitofrontal cortex (OFC) has been investigated regarding ΔFosB induction following chronic cocaine exposure (86). This area is thought to have normal roles regarding decision-making (104), expectation of reward or punishment (105), and judgement (106). Interestingly, ΔFosB levels were significantly greater following cocaine self-administration compared to when it was experimentally injected (86). By the use of behavioral decision-making tests, ΔFosB induction in the OFC was shown to be related to cognitive change. Moreover, chronic dosing caused tolerance to the dysfunctional changes of acute exposure, and subsequent studies have shown ΔFosB induction in the OFC to sensitise animal models to the locomotive properties of cocaine (107).

Table 1. Correlating cellular and molecular effects of ΔFosB targets with behavioral changes following chronic cocaine exposure.

ΔFosB-induced target	Cellular effect	Behavioral effect
GluR2	Decreased glutamatergic transmission	Increased drug reward
CDK5	GluR1 synaptic protein phosphorylation	Decreased drug reward
	Increased NAc dendritic branching	Decreased drug reward
NFκB	NFκB inflammatory response in the NAc	Increased drug reward
	NFκB inflammatory response in the CP	Locomotor sensitisation
	Increased NAc dendritic branching	Increased drug reward

Following chronic cocaine dosing, ΔFosB induces expression of three main downstream targets: the GluR2 AMPA subunit; Cyclin dependent kinase 5 (CDK5); and Nuclear Factor κB (NFκB). The ΔFosB-mediated expression of these three targets results in further cellular and molecular changes with correlated behavioral manifestations (see text for references). CP, Caudate-Putamen; NAc, Nucleus Accumbens.

Psychologically, individuals who experience tolerance to the cognitive impairments of acute cocaine exposure are significantly more likely to become chronically dependent (108). This premise illustrates the importance and implications of the above findings (86). In this study, behavioral tolerance was mediated by specific molecular changes. Increased expression of substance P, $GABA_A$ and metabotropic glutamate subunit 5 receptors were observed. Furthermore, these changes were inhibited if ΔJunD (a ΔFosB antagonist) was given, strengthening the probability of these changes being ΔFosB-mediated. It was concluded that ΔFosB expression in the OFC may promote the psychologically addicted state, whilst in the NAc it promotes addiction by incentive and reward potentiation (physical addiction) (86).

Epigenetic alterations

Recent studies have explored the influence of ΔFosB in epigenetics, namely its role in changes in genetic expression through DNA or histone modification (109–111). Given the role of ΔFosB as a transcription factor, it is likely that some of the molecular and behavioral changes are ultimately due to epigenetic alteration.

Whilst ΔFosB is expressed following chronic drug exposure, it is well established that c-Fos (another Fos family transcription factor) is implicated in the acute phase (10,12). Using amphetamine, Renthal et al. found that the proposed role of ΔFosB as a ''molecular switch'' included repression of c-Fos (112). This resolves the issue of the previously unexplained c-Fos downregulation following repeated drug exposure. The mechanism of c-Fos repression was found to involve epigenetic mechanisms, namely the repression of mRNA by histone deacetylase 1 (HDAC1) enzymes acting on the promoter sequence (112). This led to deacetylation of histones, preventing c-Fos gene transcription. Moreover, HDAC1 KO tissue samples were found to lose this amphetamine-induced repression (112).

Multiple epigenetic pathways are suggested to occur in unison. For example, chronic amphetamine exposure has been shown to potentiate histone H3 methylation of c-Fos promoter genes, repressing gene activity (112). In addition, histone methylation observed in chronic cocaine use causes downregulation of lysine dimethyltransferase G9a (a histone methyltransferase enzyme) (113). This enzyme has been identified as essential in NAc dendritic spine expansion following chronic drug exposure. Critically, this methylation activity was regulated by ΔFosB (113).

Changes in DNA methylation status are additionally implicated. It has been shown that the transcriptional repressor methyl CpG binding protein 2 (MeCP2) regulates behavioral changes following administration of cocaine and amphetamine (114,115). Im et al. suggest that cocaine-stimulated MeCP2 represses microRNAs miR-212 and miR-132, which reduces the miRNA repression of brain derived neurotrophic factor (BDNF) (i.e. a process of disinhibition to increase BDNF and promote cocaine intake) (115). However, this hypothesis is controversial as these microRNAs may also inhibit MeCP2 (115), and contrasting studies have shown cocaine to stimulate miR-212 and miR-132 (116). Furthermore, these findings implicating a MeCP2-BDNF pathway are not reproduced using opiate models (117). The epigenetic processes regarding MeCP2 in psychostimulant addiction are clearly complex and must be fully resolved. Implicating ΔFosB with MeCP2 changes, Anier et al. show that both acute and repeated cocaine administration led to *FOSB* promoter-associated CpG island hypomethylation, decreased MeCP2 binding and led to transcriptional activation of the *FOSB* gene in the NAc (111).

ΔFosB as a therapeutic biomarker

The strong correlation between chronic drug exposure and ΔFosB provides novel opportunities for targeted therapies in addiction (118), and suggests methods to analyze their efficacy (119). Over the past two decades, research has progressed from identifying ΔFosB induction to investigating its subsequent action (38). It is likely that ΔFosB research will now progress into a new era – the use of ΔFosB as a biomarker. If ΔFosB detection is indicative of chronic drug exposure (and is at least partly responsible for dependence of the substance), then its monitoring for therapeutic efficacy in interventional studies is a suitable biomarker (Figure 2). Examples of therapeutic avenues are discussed herein.

Evaluating the addictive profile of a drug

The knowledge of ΔFosB induction in chronic drug exposure provides a novel method for the evaluation of substance addiction profiles (i.e. how addictive they are). Xiong et al. used this premise to evaluate the potential addictive profile of propofol (119). Propofol is a general anaesthetic, however its abuse for recreational purpose has been documented (120). Using control drugs implicated in both ΔFosB induction and addiction (ethanol and nicotine), similar ΔFosB expression was apparent when propofol was given to rats. Moreover, this cascade was shown to act via the dopamine D1 receptor in the NAc, suggesting that propofol has abuse potential (119).

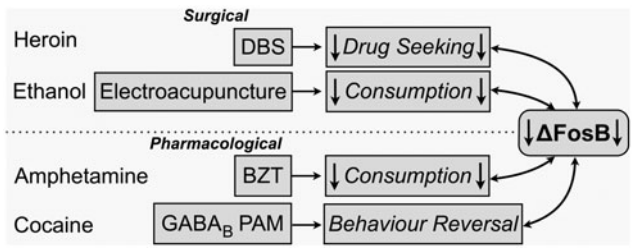

Figure 2. ΔFosB: a biomarker for therapeutic efficacy? Given that ΔFosB is induced following chronic drug exposure, it can be used to evaluate the efficacy of therapeutic intervention. This uses the premise that if a therapy is efficacious in treating addiction, ΔFosB levels should decrease. Shown here are examples of two surgical and pharmacological interventions for addiction in animal studies: deep brain stimulation (DBS) in heroin-dependent models; electro-acupuncture in ethanol-dependent models; dopamine uptake inhibitor benztropine (BZT) in amphetamine-dependent models; and a $GABA_B$ positive allosteric modulator (PAM) in cocaine-dependent models (see text for references). All four examples have different mechanisms of action to cause a desired behavioral effect. Moreover, a decrease in ΔFosB levels was correlated with behavioral alterations in the use of all four therapies.

Deep brain stimulation

A recent study of heroin administration in rats has evaluated the effects of deep brain stimulation (DBS) on the NAc (121). DBS attenuated drug-seeking behaviors, and was well correlated with a significant decrease in ΔFosB expression (and an increase in pCREB) (121). Whilst this idea of using DBS for drug addiction is in its infancy, it has potential as an intervention for treating and preventing heroin relapse.

Electroacupuncture

A further physical intervention recently studied is that of electroacupuncture. Li et al. trained rats to chronically self-administer ethanol, causing addiction and increased ΔFosB expression (122). A control cohort with sucrose exposure was also used. After addiction was established, 100 Hz electroacupuncture was administered in the ST36 region of the hindlimb. This was found to significantly decrease both ethanol consumption and ΔFosB expression in the NAc, VTA, PFC and striatum, whilst no changes were observed in the sugar-exposed control animals. Moreover, the study showed that the efficacy of electroacupuncture was correlated with ΔFosB down-regulation (122).

$GABA_B$ modulation

A pharmacological example of a potential intervention in drug-addicted patients is that of $GABA_B$ positive allosteric modulators (PAMs) (123). As previously described, GABAergic inhibitory neurons are the principal cells of the NAc (8). The study found the use of $GABA_B$ PAM 'GS39783' in mice diminished both the acute and chronic behavioral effects of cocaine (123). ΔFosB expression was inhibited in the dorsal striatum (although inhibition of CREB was far more significant). This reversal of behavioral changes by use of $GABA_B$ PAMs is also reported in other studies (57).

Dopamine blockade

A recent study raised the concept of blocking the initial ΔFosB expression witnessed in repeated drug exposure (124). ΔFosB induction in many areas is mediated by dopamine receptors, and thus dopamine neurotransmission is critical for these molecular and behavioral changes (52,61). With this premise, one group utilized a derivative of N-substituted benztropine (BZT) to block the dopamine transporter with high affinity in rodents conditioned to self-administer amphetamine chronically (124). In mice undergoing conditioned place preference associated with amphetamine treatment, the BZT analog prevented ΔFosB accumulation in the NAc, and reduced the levels of self-administration. Thus, it was concluded that BZT analogs may have a role in the treatment of addiction (124).

AP-1 DNA binding

AP-1 complexes are thought fundamental in both behavioral and molecular changes associated with addiction (20). Therefore, their initial inhibition may alleviate any drug-induced change. A recent study has investigated this, using a selective inhibitor for the signal-regulated kinase pathway (SL327) following cocaine exposure (125). The use of SL327 reduced the DNA-binding affinity of AP-1 complexes, and hence decreased genetic change. Importantly, SL327 also decreased levels of all Fos family proteins, including ΔFosB. However, a major limitation affecting interpretation of this intervention is that SL327 was given as a pre-treatment, and thus the applicability of this as a therapy is restricted. Further studies must evaluate a possibility of its use in a post-addicted state.

Sirtuins

It has been shown that both cocaine and morphine administration with consequential induction of ΔFosB in the NAc increases sirtuin 1 and 2 levels (Sirt1/2) (75,126). Using chromatin immunoprecipitation, Renthal et al. show that Sirt 1 and 2 are target genes of ΔFosB induction through histone acetylation (75). Sirt1/2 expression was additionally linked to increased excitability of NAc medium spiny neurons. Consequently, the authors suggest the possibility of Sirt-inhibitors as a potential therapeutic intervention. Further studies using ΔFosB as a suitable biomarker must commence to evaluate this prospective therapy.

Conclusions

ΔFosB is an essential transcription factor implicated in the molecular and behavioral pathways of addiction following repeated drug exposure. The formation of ΔFosB in multiple brain regions, and the molecular pathway leading to the formation of AP-1 complexes is well understood. The establishment of a functional purpose for ΔFosB has allowed further determination as to some of the key aspects of its molecular cascades, involving effectors such as GluR2 (87,88), Cdk5 (93) and NFκB (100). Moreover, many of these molecular changes identified are now directly linked to the structural, physiological and behavioral changes observed following chronic drug exposure (60,95,97,102). New frontiers of research investigating the molecular roles of ΔFosB have been opened by epigenetic studies, and recent advances have illustrated the role of ΔFosB acting on DNA and histones, truly as a ''molecular switch'' (34).

As a consequence of our improved understanding of ΔFosB in addiction, it is possible to evaluate the addictive potential of current medications (119), as well as use it as a biomarker for assessing the efficacy of therapeutic interventions (121,122,124). Some of these proposed interventions have limitations (125) or are in their infancy (75). However, it is hoped that some of these preliminary findings may lead to innovative treatments, which are much needed in addiction.

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Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this paper.

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