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Review

An important new chapter in Neuroscience

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Abstract

Neuroscience began an important new chapter in the 1980s when it was demonstrated that the induction of cFos occurred in response to the stimulation of acetylcholine receptors in neuron like cells. Transcription of c*fos* commenced within minutes and involved an influx of extracellular Ca^{2+} through voltage-sensitive calcium channels. Neuronal activity in many neuron types and brain regions led to the induction of many genes on various time scales. The first to be activated were called immediate early genes (IEGs), which include the Fos family c*fos*, *fos*B, *fra*1, *fra*2, and several isoforms. A short form of *fos*B called ΔFosB resisted degradation and was thought to play a role in inducing changes in neurons associated with addiction. The protein products of many IEGs act as transcription factors which are important in neurons of the central nervous system for their roles in neuronal plasticity, exemplified by learning and memory, addiction and several neuropsychiatric disorders such as depression. In this article experimental data and the biochemical processes underlying the pathways which lead to such transcription are described as a prelude to modeling.

Keywords: ΔFosB, IEG, nucleus accumbens, dopamine, glutamate, psychostimulants, addiction, modeling

1. Introduction

Addictions to drugs and other stimulatory agents constitute enormous medical and social problems. According to Nielsen (2012) there were over 20 million people in the USA classified as substance abusers including over 1 million people addicted to cocaine, 350,000 addicted to heroin, over 1 million prescription opiate abusers and over 17 million people were alcoholics. These data translate to an incidence of about 1 in 15 individuals who are addicted to various drugs but there are also serious behavioral addictions, such as those involving the primary reinforcers food and sex, with numbers which are hard to estimate. Addiction to all forms of electronic or digital media is self-evident, especially the seemingly obsessive use of smartphones.

The neurobiological foundations of such addictions have been the focus of many laboratories for the last few decades. It has become clear that the links between neuronal activity and the expression of many genes in various regions of the brain contribute to the development of an addictive state (for example, Berke and Hyman, 2000; Cruz et al., 2015; Gajewski et al, 2016; Hyman and Malenka, 2001; Koskela et al., 2017; Nestler, 1992, 1997, 2001a,b, 2004a,b, 2014; Renthal and Nestler, 2009; Robison and Nestler, 2011). Heller et al. (2014) succinctly stated that chronic drug abuse regulates transcription factors, chromatin-modifying enzymes and histone posttranslational modifications in discrete brain regions. Furthermore, such genetic activation leads to morphological changes in neurons including alterations in spine densities and properties, mainly studied in the medium spiny neurons of the nucleus accumbens (for example, Anderson & Self, 2017; Cahill et al., 2016; Dos Santos et al., 2017; Grueter et al., 2013; Khibnik et al., 2016; Robinson and Kolb, 2004). Such morphological changes may have roles in the development of brain circuits for addictive behavior (for example, Anderson & Self, 2017; Grueter et al., 2013; Nestler, 2001a, 2001b, 2004a, 2013, Russo et al., 2010).

1.1 An important new chapter in Neuroscience

An important new chapter in Neuroscience began in the 1980s and early 1990s. Greenberg et al. (1986b) demonstrated the neurotransmitter mediated induction of cFos in response to stimulation of acetylcholine receptors in PC12 cells. Transcription of c*fos* commenced within minutes and required an influx of extracellular Ca^{2+} through voltage-sensitive calcium channels. It was soon discovered that neuronal activity or its associated processes in many neuron types and brain regions led to the induction of many genes on various time scales (Morgan & Curran, 1986; Dragunow et al., 1987; Morgan et al., 1987; Sonnenberg et al, 1989; Winston et al., 1990; Young et al., 1991). The first to be activated, often within 20 minutes or sooner, were called immediate early genes (IEGs), which include, inter alia, the Fos family c*fos*, *fos*B, *fra*1, *fra*2, and several isoforms, and the Jun family c*jun*, *jun*B and *jun*D. The protein products of many IEGs re-enter the nucleus and act as transcription factors for many other less rapidly induced genes. It has been demonstrated that many IEGs are important in neurons of the central nervous system for their roles in instigating paths to neuronal plasticity (Hughes & Dragunow, 1995) exemplified by learning and memory and as seen above, addiction. In addition, they have been implicated in neuropsychiatric disorders such as depression (Nestler, 2015a; Gajewski et al., 2016) and in both the benefits and deleterious side effects of drugs used to treat schizophrenia (Robertson, 1995).

With many acute stimuli, such as those that result from psychostimulants such as cocaine and amphetamines or electroconvulsive seizures, their activation was for the most part transient, including that of the shortened form of *fos*B called Δ*fos*B which arises from alternative splicing (Black, 2003; Marinescu et al., 2007; Alibhai et al. 2007) whose protein product has a molecular mass of 33 kDa. However, under chronic stimulus application, modified forms of ΔFosB of 35-37 kDa persisted for much longer time periods and were hypothesized to lead, inter alia, to structural changes in neuronal morphology. Such changes in neurons of several brain regions with various regimes of cocaine administration were detailed in Maze & Russo (2010).

There are many brain regions in which the expression of ΔFosB has been demonstrated. Nestler et al. (1999) listed several regions, including prefrontal cortex, hippocampus, LC and striatum, in which chronic cocaine, amphetamines, nicotine, opiates, ECS, antidepressants, antipsychotics and stress may give rise to Δ*fos*B induction; Perrotti et al. (2008) and Nestler (2008) documented the relative strengths of expression of ΔFosB in many regions with chronic application of cocaine, morphine, Δ^9-THC (the psychostimulant component of marijuana) and ethanol; and Pitchers et al. (2010) tabulated many brain regions where Δ*fos*B expression arises in relation to sexual experience. The roles of ΔFosB in prefrontal cortex and hippocampus in addiction and depression have recently been investigated by Gajewski et al. (2016). Related articles on ΔFosB and psychiatric disorders are those of Vialou et al. (2010), concerned with stress resilience and mechanisms of antidepressants, Robison et al. (2014) on mechanisms of antidepressants and Vialou et al. (2014) on the role of ΔFosB in stress and depression.

In this article the main focus is the stimuli that lead to the activation of signaling pathways and the subsequent activation of transcription factors with the resulting production of mRNA and protein. Anatomically most of the results discussed pertain to the striatum, particularly the nucleus accumbens which along with the VTA is considered an important component of the brain reward system (Nestler, 2004a). There are many stimuli apart from the broadly defined neuronal activity, which result in such activation, including neurotransmitters, synaptic activation, electrical stimulation or depolarization by for example potassium ions, drugs including prescribed medications and drugs of abuse which can lead to addiction, substances which are natural rewards such as food, water and sex as well as stress and debilitating mood changes such as depression. Learning and memory processes also lead to such genetic activation and subsequent morphological changes in neurons as do LTP and LTD (Russo et al., 2010).

There is a large degree of overlap in the molecular underpinnings of the biochemical pathways involved in transcription induced by diverse stimuli including neuronal activity, drug stimuli, natural rewards, LTP/LTD, learning and memory processes, stress and mood. In most of these the main cell membrane elements activated are dopamine and glutamate receptors as well as voltage sensitive Ca^{2+} channels. The most frequently investigated brain regions are the striatum and the hippocampus, both of which have been explored in relation to LTP/LTD. Some interesting general principles have emerged as described clearly by Nakano et al. (2010) who developed a mathematical model of some signaling pathways in MSN including the regulatory protein DARPP-32 (see subsequent section).

For example, cortico-striatal stimulation of MSNs leads to LTD with only glutamatergic inputs, which lead to Ca^{2+} influx, but may lead to LTP if there is accompanying dopaminegic input. However, if the Ca^{2+} input is strong enough by itself it may lead to LTP so that there are two modes of LTP - glutamate (Ca^{2+}) augmented by dopamine and Ca^{2+} alone. The main element involved in the plasticity and included in Nakano et al. (2010) model here is phosphorylated AMPA receptors which are inserted in the postsynaptic membrane resulting is a greater conductance. LTP at hippocampal to prefrontal cortex glutamatergic synapses exhibits similar properties with dopamine release from terminals arising from the VTA (Jay et al., 2004).

Most of the present article concerns signaling pathways in MSNs which have different components from those of hippocampal neurons (West et al., 2002; Deisseroth et al., 2003) in that dopamine receptors are absent in the latter. Nevertheless, there are sometimes depicted connections from VTA to striatum as in Berton & Nestler (2006) and (Cooper et al. 2003, Figure 9.1). Another difference is that DARPP-32 is abundant in MSNs but practically absent in hippocampus and other brain regions (Walaas et al., 2011; Yger & Girault, 2011).

1.2 Fos family

The emphasis in the experimental results examined in this article is on the IEG family Fos. **Table 1** lists the molecular masses of the most commonly studied Fos family proteins from a sample of studies.

The induction of Fos family genes has been studied quantitatively in several brain areas with various means of elicitation, including the application of psychostimulants such as cocaine, amphetamine and cafeine, and electrical stimuli such as electroconvulsive therapy. The brain regions most frequently studied are the prefrontal cortex, hippocampus and the basal ganglia which contain the dorsal striatum (caudate nucleus and putamen) and the ventral striatum consisting of the nucleus accumbens and the olfactory tubercle. Subsidiary, but not less important, elements are globus pallidus, ventral pallidum, substantia nigra and subthalamic nucleus.

Table 1: Molecular masses in kDa of Fos family proteins

Protein	Molecular masses (Expt.)	Mean	Sources
cFos	52, 55, 58	55	a, b, c
FosB	46-48, 45, 46, 45	45.75	a, b, c, d
Fra1, Fra2	41, 41, (42, 40), 41	41	a, b, c, d
ΔFosB	33, 33	33	a, c
$\Delta FosB^{35}$	35	35	a, c
$\Delta FosB^{37}$	37	37	a, c

a, Perrotti et al. (2004); b, Hiroi et al. (1998); c, Chen et al. (1997); d, Nye et al. (1995)

The striatal regions contain mainly GABA-ergic medium spiny neurons (MSN, also called striatal projection neurons or SPN) which receive dopaminergic inputs from the midbrain structures of the substantia nigra pars compacta and the ventral tegmental area as well as glutamatergic inputs from the prefrontal cortex (McGeorge & Faull, 1989; Cummings, 1993), thalamus (Berendse & Groeneweg, 1990), amygdala (McDonald, 1991) and hippocampus (Kelley & Domesick, 1982; Floresco et al., 2001). According to Surmeier et al. (2007) about 40% of these glutamatergic afferents come from each of the prefrontal cortex and the thalamus. At the MSNs, the synapses of glutamatergic inputs occur on the spine heads whereas dopaminergic inputs are positioned on the spine necks (Yager et al., 2015). MSNs also receive cholinergic inputs and GABA inputs from interneuronal sources. Kreitzer (2009) contains a review of MSN properties.

Many anatomical maps have been published over the last twenty or so years which depict connections involving striatal neurons in both human and rodent brains. Although they have features in common, they have different emphasis depending on whether they are focused on addiction, LTP/LTD/reward or mood, especially depression. The anatomical arrangement of the brain circuits pertaining to the investigations of interest and the main connecting structures are depicted for a human brain in **Figure 1**, which is taken from Treadway & Zalb (2011). Diagrams for circuits involved in mood, including depression, usually include the serotonergic connections from the dorsal raphe ..

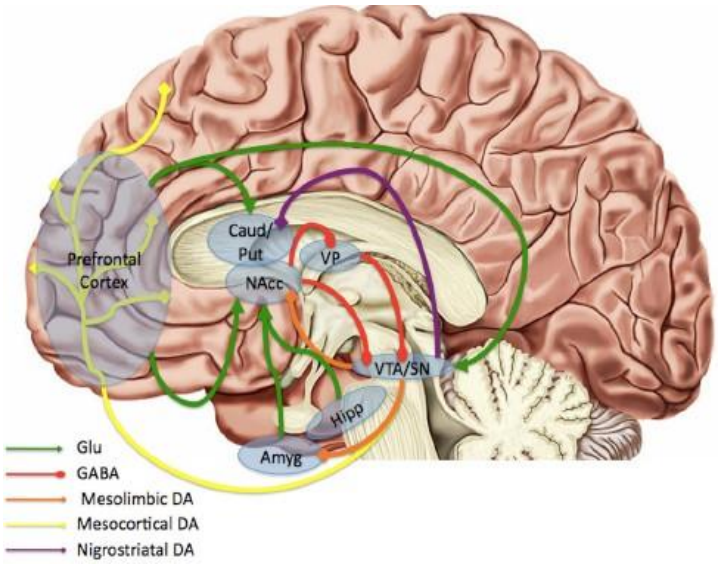


Figure 1 *Showing the basic anatomical components of the human brain involved with the MSNs of the striatum. In these neurons, for example, application of psychostimulants, leads to activation of neurotransmitter receptors, which may cause signaling cascades via second messengers. Such signaling may give rise to cytoplasmic activation at synapses and subnuclear transcription of IEGs and other genes involved in long term synaptic plasticity and other morphological changes. Elements indicated: Prefrontal cortex, caudate nucleus and putamen (Caud/Put), ventral pallidum (VP), nucleus accumbens (NAcc), ventral tegmental area/substantia nigra pars compacta (VTA/SN), hippocampus (Hipp), amygdala (Amyg). From Treadway & Kalb (2011).*

nucleus and noradrenergic connections from the locus ceruleus - as in Nestler et al. (2002), Berton & Nestler (2006) and Nestler (2015b). Serotonin receptors on MSN and their input synapses also play a role in L-dopa induced dyskinesia (Picconi et al., 2018). Diagrams showing circuitry most important for drug addiction, with varying degrees of detail for rat brain, are given in Koob et al. (1992), Nestler (2004a), Koob & Nestler, (1997), Nestler (2001a) and Yager et al., (2015). Similar diagrams depicting reward circuits involving the NAc and VTA are those of Robison & Nestler (2011) and Russo & Nestler (2013). In summary these diagrams mainly show GABAergic afferents from MSNs in the striatum, glutamatergic afferents from frontal cortex, amygdala, hippocampus and dopaminergic afferents from VTA/SNc. The map of Yager et al. (2015) shows clearly the separate functions of SNpc and SNpr in relation to the direct and indirect pathways from striatum to Gpi/SNpr (see subsequent sections). There are a few details in **Figure 1** which need some elucidation: the olfactory tubercle which is part of the ventral striatum is not shown in its location just ventral to the nucleus accumbens (Xiong & Wesson, 2016) nor is the thalamus included; also, the ventral tegmental area and the substantia nigra pars compacta are not shown as distinct regions.

2. Signaling pathways and the c*fos* and *fos*B promoters

In many experiments mRNA is measured, often in addition to protein. The basal levels of Fos family proteins are often reported to be low, especially cFos (Herrera & Robertson, 1996). Basal levels of ΔFosB^{35} and ΔFosB^{37} (sometimes called chronic Fras), however, exhibit regional differences and may be quite high in some brain regions, including NAc and striatum (Hope et al., 1994b; Vialou et al., 2012) but low in frontal cortex (Chen et al., 1995; Ulery et al., 2006) and even lower in thalamus and hypothalamus. The high levels in NAc and striatum indicate that ΔFosB may accumulate under normal physiological conditions and not just as the result of extreme stimulation as occurs with psychostimulants or ECS. Interestingly, in mice, Vialou et al., (2010) discovered that such basal levels in the NAc predict initial vulnerability to social defeat stress, and further, that the degree of ΔFosB induction in response to chronic stress determines how well an individual will cope with that stress. The observation of lower levels of ΔFosB in the NAc of depressed humans indicates that these findings for

Figure 2 *Schematic of the principal elements of the cfos promoter. From Kovács (1998).*

mice could be relevant to theories of clinical depression. For a more detailed description see Nestler (2015a).

Although the basal levels of the IEG cFos expression are usually relatively low (Morgan et al., 1987), c*fos* is rapidly activated in MSNs of the NAc by many acute stimuli including seizure and psychostimulant drugs such as amphetamine and cocaine (Sonnenberg et al., 1989; Graybiel et al., 1990; Young et al., 1991; Hope et al., 1992; Hope et al., 1994a, b).

Transcription of a gene, the process whereby messenger RNA is assembled according to code from DNA, is effected by the setting up of the transcription machinery and the binding of transcription factors to elements within a gene's promoter. Knowledge and understanding of the structure and function of the c*fos* promoter have increased greatly since those early discoveries. Cruz et al. (2015) review many aspects of c*fos* transcription; early descriptions were reviewed in Schuermann (1994).

The four principal elements of the c*fos* promoter are as follows and are schematically shown in **Figure 2** which is adapted from Kovács (1998) and Sng et al. (2004). The latter reference also depicts the structure of the c*jun* promoter.

(1) The SIE (sis-inducible element) which is activated by growth factors such as PDGF.
(2) The SRE (serum response element) which is activated by serum, growth factors and Ca^{2+}
(3) The AP-1 site to which bind dimers of proteins such as fos/jun
(4) The Ca/CRE (Ca^{2+} /CAMP response element) which is activated by Ca^{2+} or cAMP. This is usually abbreviated to CRE.

For more details of the structure of elements of the c*fos* promoter, (see Gius et al., 1990; Metz & Ziff, 1991; Ghosh et al., 1994; Cochran, 1995; Robertson et al., 1995; Sharrocks & Shore, 1995; Johnson et al., 1997; Hipskind & Bilbe, 1998; Kovács, 1998; Hyman et al., 2006 and Hong & Ping, 2009).

The depiction of the c*fos* promoter in **Figure 2** omits the details of the actual geometric relation between the promoter elements and DNA structure, none of which are described in the references of the previous paragraph. The DNA structure involves nucleosomes which are groups of histone proteins about which DNA is wrapped. These are further described in subsequent sections and exemplified in their relation to c*fos* promoter elements in the **Figures 3C** and **3D**. The chemical states of the histone proteins play essential roles in the instigation and termination of transcription (Mahadevan et al., 1991; Tsankova et al., 2004; Tsankova et al., 2007; O'Donnell et al., 2012).

The *fos*B and c*fos* promoters are located on different chromosomes, being on chromosomes 7 and 12, respectively, in mouse (Lazo et al., 1992) but they have similar structures and are both activated rapidly by the same acute stimuli. The appearance of FosB protein lags that of cFos and in the acute case is usually shown as being of less magnitude (Hope et al, 1994a; Nestler, 2004b).

2.1 Intracellular components

Ca^{2+} enters the cytoplasm of MSNs as a consequence of activation of NMDA receptors by glutamatergic inputs from several regions including the PFC, hippocampus and amygdala (Grace et al., 2007) as well as through L-type Ca^{2+} channels. ERK activation plays a major role in IEG transcription (Sgambato et al., 1998; Brami-Cherrier et al., 2009). If the level of intracellular Ca^{2+} is high enough, which may include contributions from internal stores, ERK-dependent activation of c*fos* occurs via the phosphorylation of Elk1 which binds with SRF to the SRE and through phosphorylation of CREB which binds to the CRE. Flavell & Greenberg (2008) cite evidence that Elk1 phosphorylation by ERK is critical for glutamate mediated c*fos* activation.

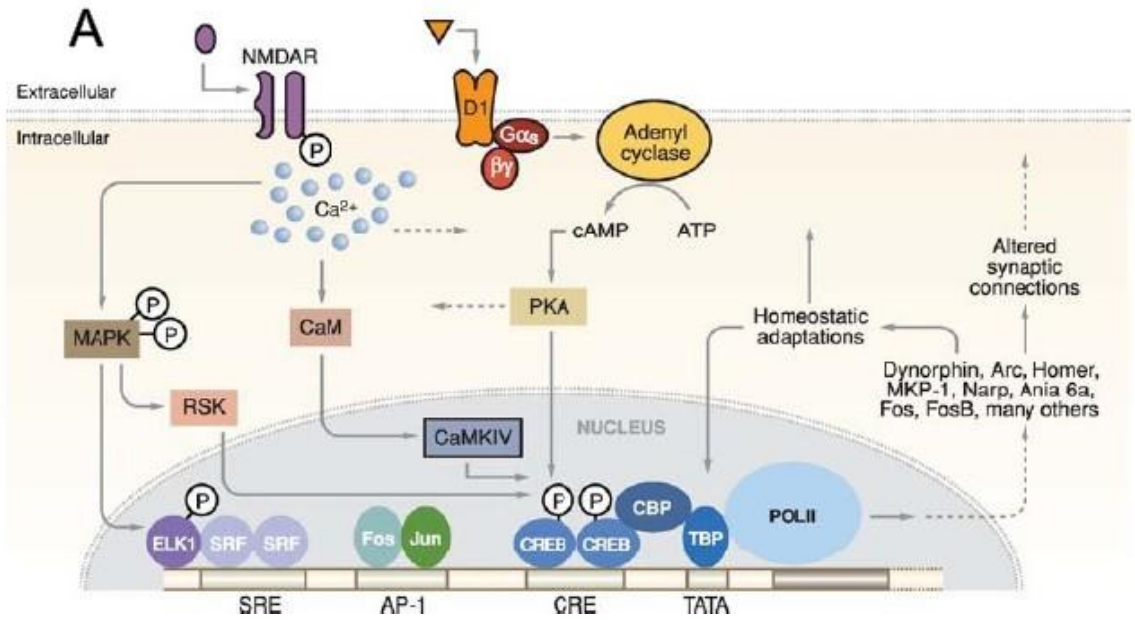
Activated ERK is translocated to the nucleus within 10 minutes of cocaine injection (Valjent et al., 2000). Contributions to CREB phosphorylation may also come from the CaMK pathway and it has been found (see figure in Tuckwell, 2019) in hippocampal cells that these arise more rapidly than those from the ERK/MAPK pathway (Wu et al., 2001; Cruz et al., 2015). Furthermore, it was found, in transgenic mice, that maximal activation of c*fos* in vivo requires cooperation among several elements on the c*fos* promoter, including SRE, the rarely mentioned SIE (see for example Hipskind & Bilbe, 1998), the AP-1 binding element, and CRE (Robertson et al., 1995; Bito et al., 1997).

Interestingly, calcium from different sources may activate distinct signaling pathways. For example, activation of L-type Ca^{2+} channels lead to SRE- or CRE-dependent transcription, whereas activation of NMDA receptors leads primarily to SRE-dependent transcription (Ghosh et al., 1994). In fact, calcium increases which lead to CREB binding to the CRE have been claimed to be preferentially originating from L-type Ca^{2+} channels (Bading et al., 1993; Hardingham et al., 1997). The latter are claimed by Rajadhyaksha et al. (1999) to be in fact necessary for glutamate-mediated CREB phosphorylation and c*fos* transcription in striatal neurons, as activated NMDA receptors give rise to sodium currents which depolarize the L-type Ca^{2+} channels.

Simplified schemes of the molecular events, called signaling pathways, leading to c*fos* and other IEG transcription in NAc MSN, are shown in **Figure 3**, A-D, taken respectively from Hyman et al., (2006), Cruz et al., (2015), Brami-Cherrier et al. (2005) and Brami-Cherrier et al. (2009). Three of these, A-C, show the D1 dopamine receptor and the NMDA glutamate receptor whose activation results in signaling pathways which lead to the activation of elements on the c*fos* promoter. Shown in all four diagrams are the elements SRE and the CRE which are mostly responsible for the induction of IEGs in striatal MSNs. An AP-1 element is shown only in 3A and in addition pathways leading to the modification of histones are shown in 3C and 3D.

Figure 3A is based on earlier diagrams in Berke & Hyman (2000) and Hyman & Malenka (2001). Similar versions of these signaling pathways and promoter elements are described in McClung & Nestler (2008), Matamales & Girault (2011), Cruz et al. (2013) and Cadet (2016).

The role of cAMP activation of the CRE indicated in **Figures 3A** and **3C** is controversial. Cruz et al. (2013) cite evidence (Mattson et al., 2005) that c*fos* expression is not mediated by the cAMP pathway. In a later article, Mattson et al. (2007) point out that this is especially the case in neurons containing D2 receptors whose stimulation actually reduces cAMP concentrations. However, conclusions such as these may be specific for certain stimuli and cell types. The topic is discussed fully in the sequel.



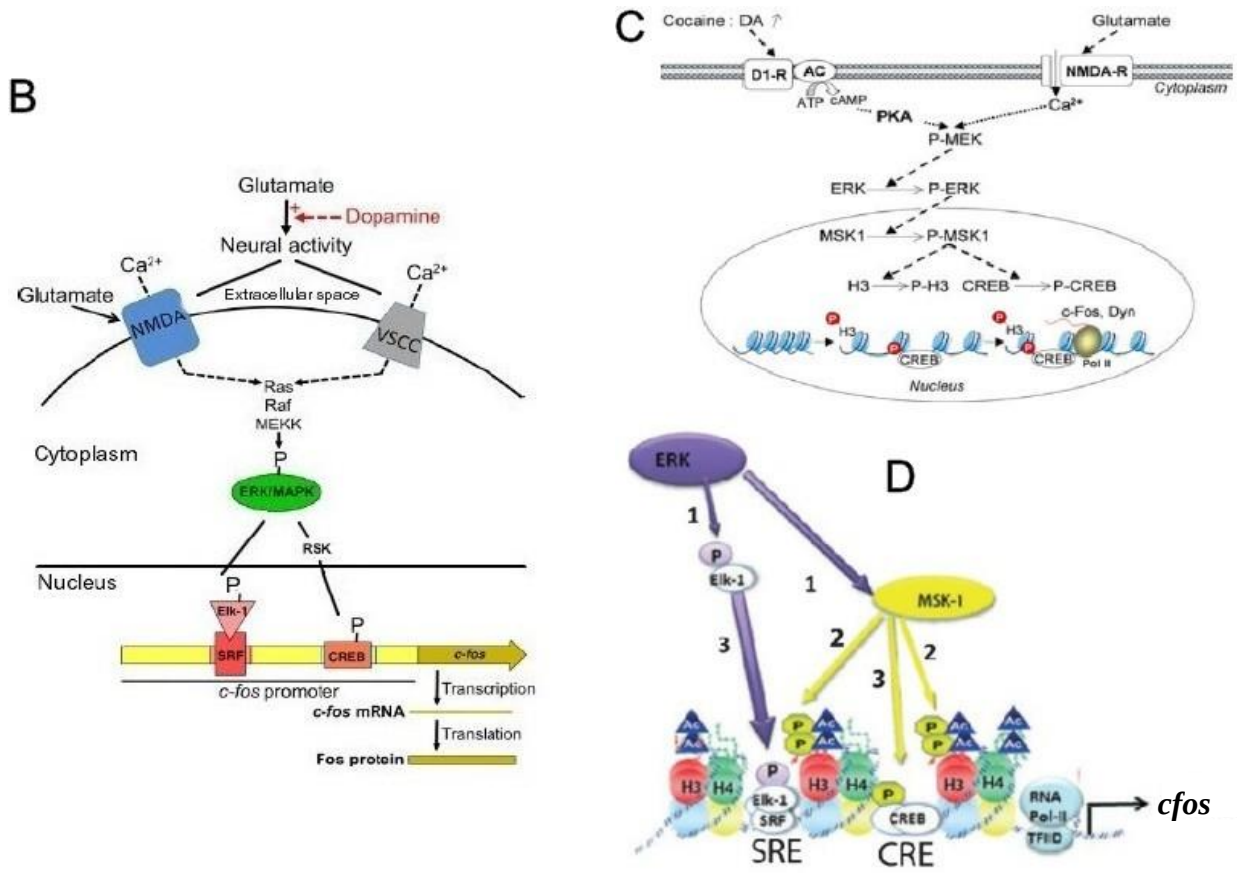


Figure 3 *Four simplified schemes,* ***A-D*** *showing various signaling pathways which lead to activation, as the result of psychostimulants or ECS, of elements of the cfos promoter as well as some histone modifications (see subsequent section) in MSNs of the striatum and nucleus accumbens. In* ***A*** *the three promoter elements SRE, AP-1 and CRE are shown, whereas in the remaining schemes only the SRE and CRE are indicated.* ***A****, adapted from Hyman et al., 2006. There are two types of receptor, a D1 dopamine receptor and an NMDA glutamate receptor giving rise to three paths to activation of the CRE. (1)D1-AC-cAMP-Protein kinase A (PKA) which phosphorylates CREB on Serl33 (Hipskind and Bilbe, 1998), enabling the recruitment of the transcription factor CREB binding protein (CBP) discussed further subsequently. (2) NMDA-Ca^{2+}-phosphorylated ERK which in turn activates RSK, discussed fully in Brami-Cherrier et al. (2009), enabling it to phosphorylate CREB. (3) NMDA-Ca^{2+} -CaM-the kinase CaMKIV which phosphorylates CREB. There is one path shown which leads to activation of the SRE element, being NMDA-Ca^{2+} - phosphorylated ERK which in turn phosphorylates Elk1 which binds to an SRF dimer and activates the SRE.* ***B****, adapted from Cruz et al., 2015. As in* ***A*** *there is an NMDA receptor which when activated gives rise to Ca^{2+} entry but an additional source of Ca^{2+} comes from the voltage sensitive L-type calcium channels. Dopamine plays a potentiating role at the NMDA receptors. In the cytoplasm Ca^{2+} activates a Ras/Raf/MEKK pathway which leads to phosporylated ERK. As in* ***A*** *Elk1 is activated and leads to transcription at the SRE element whereas ERK also activates RSK to give rise to transcription at the CRE.* ***C****, adapted from Brami-Cherrier et al., 2005. As in* ***A*** *D1 dopamine receptor stimulation leads to PKA and NMDA glutamate stimulation gives rise to Ca^{2+} influx both resulting in the sequential phosphorylation of MEK and ERK in the cytoplasm followed in the nucleus by the facilitation of transcription due to phosphorylation of histone H3 and activation of CREB at the CRE. Dyn = preproddynorphin, Pol II = RNA polymerase.* ***D****, adapted from Brami-Cherrier et al., 2009. Only the final steps of paths are shown. ERK is shown phosphorylating Elk1 to activate the SRE. ERK also activates MSK1 which phosphorylates CREB to activate the CRE. In addition, MSK1 phosphorylates histone H3 at Ser10 which facilitates transcription and histone H4 is hyperacetylated. TFIID takes part in the transcriptional process with RNA Pol II.*

2.2 Neuronal activity and transcription

That neurotransmitters could lead to gene transcription in PC12 neuron-like cells was already mentioned in the Introduction. It was reported a few years later that depolarization of these cells led to c*fos* induction mediated by Ca^{2+} at the CRE (Sheng et al., 1990). Morgan & Curran (1991) contains a table listing nearly 20 kinds of stimuli that elicit c*fos* induction in the mammalian nervous system.

Later experiments on dorsal root ganglion neurons (Sheng et al., 1993; Fields et al., 1997) showed that electrical stimulation including action potentials resulted in c*fos* expression. These studies investigated the role of the temporal characteristics of increases in intracellular Ca^{2+} and found that a key variable was the time between bursts of action potentials. Large, sustained increases in intracellular Ca^{2+} produced minimal c*fos* expression. IEG activation was inversely related to the burst intervals of action potentials.

Maximal induction of c*fos* expression required the activation of both the MAP kinase pathway and CREB phosphorylation. Brief, frequently repeated bursts can induce such coordinated activation of MAP kinase and CREB to induce expression of *cfos.* The relation between spike train properties and the degree of c*fos* induction is discussed in a subsequent section. A recent study extended the analysis of the relationship between the pattern of action potentials to the induction of hundreds of genes (Lee et al., 2017).

Rises in intracellular Ca^{2+} in hippocampal neurons had long been posited to mediate c*fos* transcription after activation of glutamate receptors or voltage-sensitive Ca^{2+} channels (Lerca et al., 1992; Labiner et al., 1993). Indeed, synaptic activity has been considered as a likely primary factor in c*fos* expression (Cruz et al., 2013; Sgambato et al., 1997), which is reminiscent of the suggestion that synaptic potentials are equally or more important than action potentials in information processing (Tuckwell, 2000). Dolmetsch et al. (1998) investigated the effects of the properties of Ca^{2+} oscillations on the induction of several genes in non-neuronal cells. Of particular interest from this study are the results, shown here in **Figure 4**, showing a logistic type dependence of gene expression on intracellular steady state Ca^{2+} concentration with a half-maximal value at about 270 nM and saturating at about 525 nM.

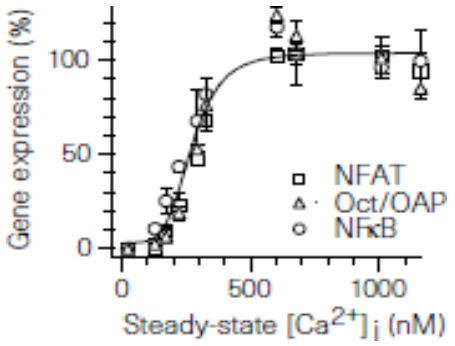


Figure 4 *Dependence of expression of three reporter genes in T cells on steady state intracellular Ca^{2+} concentration. Adapted from Dolmetsch et al. (1998).*

West et al. (2002) discuss in detail many aspects of the important roles that Ca^{2+} and its various channel types play in the transcription of c*fos* and other IEGs in neurons. Flavell & Greenberg (2008) review the signal transduction pathways whereby neuronal activity regulates gene expression through increases in intracellular Ca^{2+}. Such pathways involve not only the CRE but also the SRE.

3. Experimental results on induction of Fos family genes

This section contains a brief summary of some of the results of measurements of Fos family proteins and mRNAs in response to various stimuli, with emphasis on pschostimulants such as cocaine and amphetamine and ECS. There have been a very large number of such experiments since the late 1980s and especially since the discovery of the important role of ΔFosB as a transcription factor (Dobrzanski et al., 1991; Nakabeppu & Nathans, 1991; Yen et al., 1991).

3.1 Induction of Fos family mRNAs

Since the 1980s, very many studies have been made on various types of cell, both neuronal and nonneuronal, with a variety of agents and stimuli that induce the expression of Fos-family genes. We are mainly concerned here with representative results for c*fos* mRNA and the mRNAs for *fos*B and Δ*fos*B.

3.1.1 *Measurements of c-fos mRNA*

According to Morgan & Curran (1991), several kinds of stimuli including some associated with neuronal activity give rise to the transient induction of c*fos* mRNA with almost identical time courses. Transcriptional activation occurs within 5 minutes and continues for 15-30 minutes. The level of mRNA reaches maximum values at 30-60 minutes post-stimulation and then declines with a half-life of about 15-30 minutes (Greenberg et al, 1985; Mitchell et al., 1986).

There are only a few articles that give line-graphs for c*fos* mRNA as most reports show the results in the form of Northern blots or bar-graphs. We illustrate firstly two line-graph results as shown in **Figure 5**. **Figure 5A,** taken from Moratalla et al. (1993), shows the level of c*fos* mRNA in rat striatum up to 6 hours after intraperitoneal injection of cocaine (25 mg/kg). The c*fos* mNRA level has a maximum at about 60 min and has returned to near baseline values by 2 hours. Similar results were obtained for *jun*B. It was also found that c*jun* was not induced and that *jun*D was constitutively expressed.

In **Figure 5B**, taken from Bading et al. (1995), is shown the time course of c*fos* mRNA in cultured neonatal hippocampal neurons after treatment with 10 μM glutamate. Transcription of c*fos* was detected 15 min after glutamate stimulation. The maximum level was attained 30-60 min after stimulation with an increase of about 60-fold, followed by a return to basal levels within 4 hours. In this experiment c*jun* and *jun*B were also found to be transcriptionally activated. It was found that in this preparation the entry of Ca^{2+} through NMDA receptors and not L-type Ca^{2+} channels was a key element in the induction of c*fos* expression.

The time course of c*fos* mRNA has been reported in several other experiments, some of which are here listed in chronological order in an abbreviated form: Chang et al. (1988), morphine, caudate- putamen; Sonnenberg et al. (1989), brain and hippocampus in response to seizure; Winston et al. (1990), cerebral cortex, successive ECS, a second stimulus did not evoke c*fos* mRNA expression at 4 hours but did after 18 hours suggesting a refractoriness for 10-14 hours; Cole et al. (1990), ECS hippocampus; Steiner & Gerfen (1993), cocaine, striatum, relation of c*fos* induction to dynorphin levels; Konradi et al. (1996), amphetamine, striatum. roles of NMDA receptors and Ca^{2+}; Badiani et al. (1999), amphetamine, c*fos* only in D1-containing MSNs in striatum, but in D2-containing MSNs as well with novelty stimulus; Kumar et al. (2005), cocaine, striatum, study of histone modifications; Mattson et al. (2007), amphetamine, nucleus accumbens; Renthal et al., (2008), amphetamine, acute and chronic, striatum. In addition, in the study by Alibhai et al. (2007) the time courses of the mRNAs of c*fos*, *fos*B and Δ*fos*B were reported as described in the next subsection.

3.1.2 *Measurements of* fos*B and* Δfos*B mRNA*

Several measurements have also been made for the mRNAs of *fos*B and Δ*fos*B. Some representative results in which line graphs were available are shown in **Figure 6. Figure 6A**, from Alibhai et al. (2007), shows the amounts (in folds relative to saline) of these two mRNAs in the first 12 hours after amphetamine was administered to rats intraperitoneally (4mg/kg). *fos*B mRNA reached a maximum of about 3 to 4 fold at about 1 hour. The amount of Δ*fos*B mRNA reaches a much higher relative level at around 10 fold in about 3 hours. Both isoforms return to basal levels at close to 12 hours. In **Figure 6B**, also from Alibhai et al. (2007), the levels are shown for the seventh day of amphetamine injection. Here the *fos*B mRNA is fairly constant at a level of roughly 2-fold and the Δ*fos*B mRNA level reaches a peak of about 3 fold at about 3 hours and then steadily declines to near basal levels.

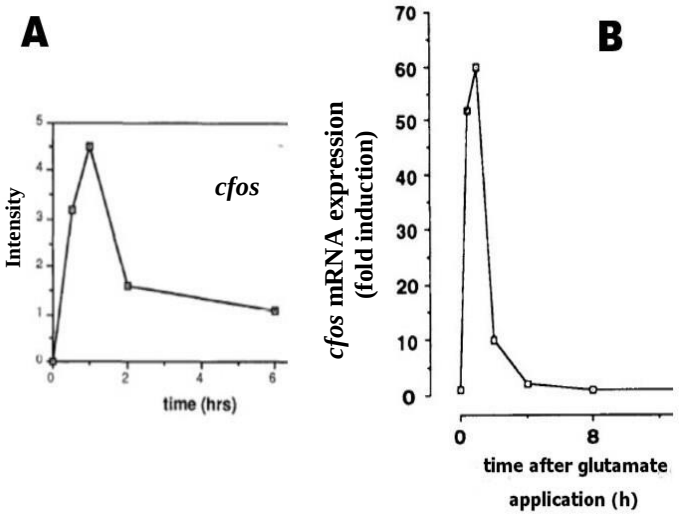


Figure 5 *Some early results for cfos mRNA.* ***A.*** *cfos expression in the striatum in response to cocaine. Adapted from Moratalla et al. (1993).* ***B.*** *Expression of cfos in cultured hippocampal neurons after treatment with glutamate, normalized to the level of mRNA of the constitutively expressed GAPDH gene. Adapted from Bading et al. (1995).*

The results in **Figure 6C**, from Chen et al. (1995), being the first in vivo set, were obtained by ECS applied to rats with measurements in cerebral cortex. These have a somewhat different character from those in **Figures 6A** and **6B** as the level of *fos*B mRNA rises rapidly to a peak of over 0.8 units in about 30 minutes and declines somewhat less rapidly to attain basal levels after about 8 hours. The accumulation of Δ*fos*B mRNA is also rapid, achieving a maximum level of 0.5 units at 30 minutes and declining to basal levels after about 4 hours. Thus in this example the level of *fos*B mRNA is relatively greater than that of Δ*fos*B mRNA, and especially so for the first 4 hours.

In **Figure 6D** are shown mRNA levels for the *fos*B and Δ*fos*B in cultured PC12 cells after application of serum. In this case the time courses for the two mRNAs are similar, with a maximum at about 2 hours and a return to basal levels at 12 hours. Here the maximum for Δ*fos*B is about 15% above that for *fos*B. However, these observations are based on a sparsity of points.

Larson et al. (2010) examined mRNA and protein levels for cFos, FosB and ΔFosB for rats administered cocaine according to various procedures and schedules. Measurements were made for NAc shell and core and CPu. For the group that self-administered with cocaine on day 18 only, the approximate mRNA levels (folds) at the end of the day were, for NAc shell, core and CPu respectively: Δ*fos*B, 13, 12, 15 and *fos*B, 9, 4 and 4. For the measurements 24 hours later, the approximate readings were Δ*fos*B, 2.5, 1.5, <1 and for *fos*B, 1, 1, 1. Thus, at all of these time points and locations the level of Δ*fos*B mRNA was greater than that for *fos*B mRNA and the level in NAc shell was greater than in NAc core.

In a related experiment, Damez et al. (2012) determined that chronic cocaine administration, followed by extended withdrawal, increases subsequent inducibility of *fos*B and Δ*fos*B in NAc but not CPu. At 28 days after either no cocaine for days 1 to 10 or cocaine on days 1 to 10, cocaine was administered. At 45, 90 and 180 minutes the

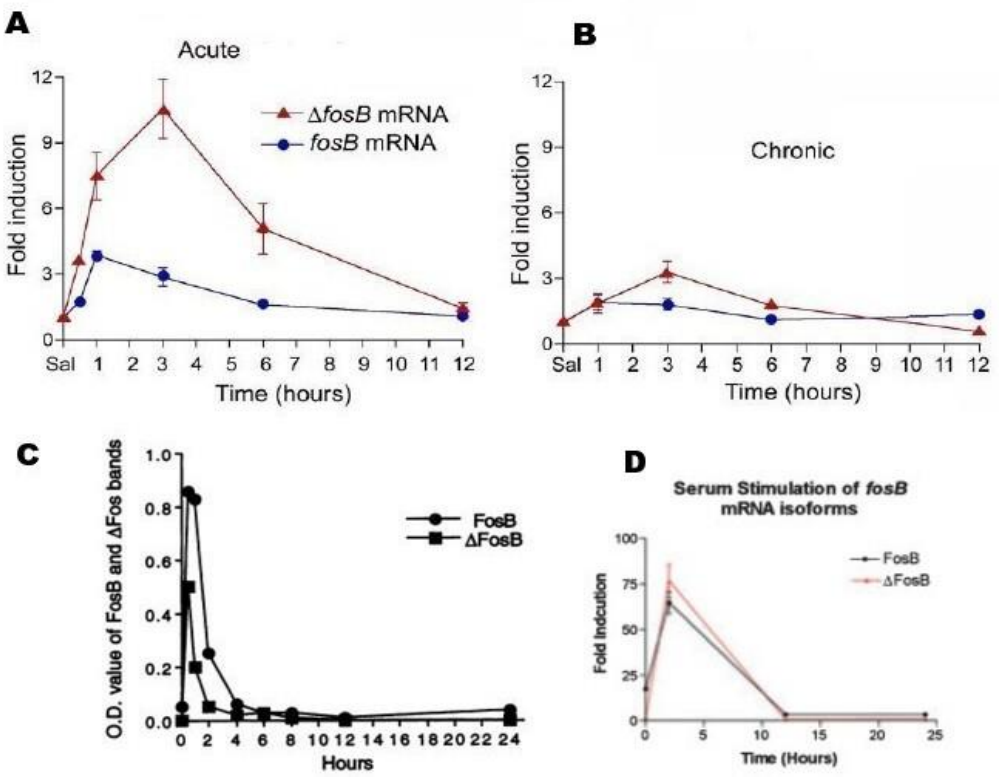


Figure 6 *Some experimental results for the measurement of fosB and ΔfosB mRNAs.* ***A.*** *Induction of these mRNAs by acute amphetamine in rat striatal neurons.* ***B.*** *Corresponding results after once daily injection of ampetamine for 7 days.* ***C.*** *Acute induction in rat cerebral cortex by ECS.* ***D.*** *Induction by application of serum to cultured PC12 cells. A and B adapted from Alibhai et al. (2007); C adapted from Chen et al. (1995); and D adapted from Carle et al. (2007).*

levels of Δ*fos*B mRNA in NAc were always larger than those for *fos*B, for both the naive and experienced groups. Furthermore, the mRNA levels of both *fos*B and Δ*fos*B were larger in the experienced group showing a priming effect.

In Alibhai et al. (2007) is also reported an interesting set of mRNA measurements showing values for c*fos*, *fos*B and Δ*fos*B at various times over a 7day period with daily amphetamine injection.

These have been plotted in **Figure 7**. In this preparation the relative level of Δ*fos*B mRNA is nearly always greater, and in the first day much greater, than that of *fos*B. For Δ*fos*B the level of mRNA is always greater at 3 hours than at 1 hour and (as expected) also greater at 3 hours than 24 hours. On days 1 and 3 the level of *fos*B mRNA decreases from hour 1 to hour 3 to hour 24, but on days 5 and 7 it is slightly greater at hour 3 than at hour 1. The overall trend of each mRNA level is down from day 1 to 7 at corresponding time points, but there are exceptions to this.

The same is true for the c*fos* mRNA levels for which in Alibhai et al. (2007) there is only a result for 1 hour. Each c*fos* result is probably near the maximum for c*fos* on each of days 1, 3, 5 and 7, these values always being above the corresponding values for *fos*B but below the corresponding values for Δ*fos*B.

A few other articles reporting *fos*B and Δ*fos*B mRNA are as follows with cell types and stimuli: Nakabeppu & Nathans (1991), cultured mouse 3T3 cells, serum and hippocampus, ECS; Dobrzanski et al. (1991), cultured cells, serum; Inoue et al. (2004), bone (osteoblasts), mechanical stress.

Noteworthy was the finding by Nakabeppu & Nathans (1991) that the relative levels of *fos*B and Δ*fos*B mRNA were about equal which differs from most of the above findings where Δ*fos*B mRNA was relatively more and sometimes much more abundant. Nakabeppu & Nathans (1991) stated that the alternative splicing mechanism, which involves competition between PTB1 and U2AF at the FosB promoter, was very efficient. Based on the data reported in several works from the Nestler laboratory

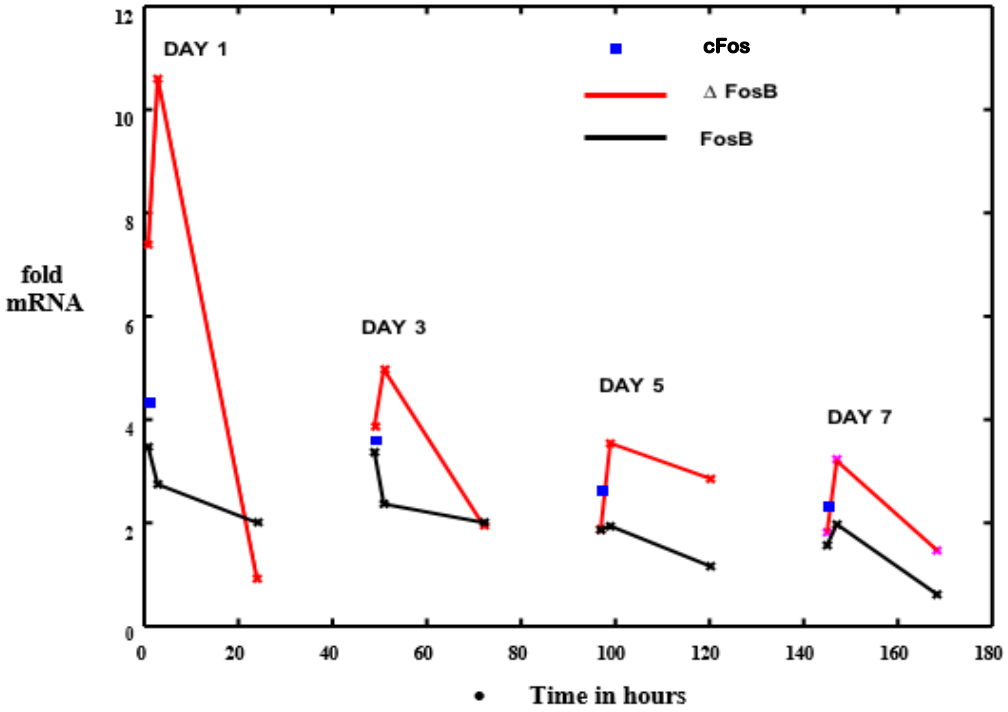


Figure 7 *Some experimental results for the measurement of cfos, fosB and ΔfosB mRNAs in rat striatal neurons, redrawn from Alibhai et al. (2007). Here, induction of these mRNAs was by once daily injection of ampetamine for 7 days. Measurements for fosB and ΔfosB are given at 1, 3 and 24 hours. cfos readings at 1 hour only, probably due to its mRNA being at a very low level after a few hours.*

it could be said in these experiments, mainly on NAc with cocaine or amphetamine, that there is a tendency for much more of the spliced product, Δ*fos*B mRNA, to be produced than that of the long form *fos*B mRNA, possibly indicating that there is not an abundance of phosphorylated PTB1 which is required for splicing (Marinescu et al., 2007; Carle et al., 2006, Alibhai et al., 2007). Some other articles which report measurements of c*fos* and other IEG mRNAs, but not Δ*fos*B, such as Persico et al. (1993) are referenced in a following section on Jun family.

3.2 Expression of Fos family Proteins

A key graphical result is shown in **Figure 8** for rat striatum which was first published in Hope et al. (1994b) and has been reproduced in many subsequent articles. In this quantitative schematic, the amounts of protein are plotted against time for cFos, FosB, the fos related antigens Fra1 and Fra2, and various isoforms of ΔFosB. In the top part of the figure the results of an acute application of cocaine (intraperitoneal 22.5 mg/kg cocaine hydrochloride) are shown. The approximate molecular masses in kDa of the various protein products were given in **Table 1** - see also Nye & Nestler (1996) and Nestler et al. (2001).

Note that experimental results such as those in Hope et al. (1994b) do not distinguish between nuclear and cytoplasmic protein. It has been deduced, however, that most of the protein detected is likely to be nuclear (Perrotti et al., 2005, 2008; Nestler, *private communication*).

A rapid rise of cFos occurs first, reaching a maximum at about 2 hours and declining to near basal levels at about 4 to 6 hours followed by a slower rise of FosB, Fra1, Fra2 and the least stable form of ΔFosB. Similar results were obtained by Sonnenberg et al. (1989) in the hippocampus after application of ECS and Young et al. (1991) in the striatum with intraperitoneal injection of cocaine. After about 4-6 hours and up to 18 hours, c*fos* cannot be induced thus exhibiting a refractory period which commences at about the same time as the maxima for FosB, Fra1, Fra2 and the 33 kDa form of ΔFosB. The possible mechanisms of this repression are various and not completely understood as discussed below. The stable isoforms of ΔFosB (35-37 kDa) are slower to increase and for the acute stimulus remain at a relatively low level.

In the lower part of **Figure 8** is shown the 35-37 kDaΔFosB protein resulting from twice daily administration of cocaine. At each of the 7 half-daily doses, there is an approximately equal increment which adds cumulatively with continued slow decay until the next dose. The result is a stair-case type function of time. $\Delta FosB^{35}$ and $\Delta FosB^{37}$ persist in the brain for many weeks following cessation of the chronic stimulus (Carle et al., 2007; Nestler, 2013). Such chronic induction of these isoforms of ΔFosB has been demonstrated for nearly all drugs of abuse in experimental animals and human addicts (Nestler, 2013). For the majority of drugs it is selective for D1-type MSN in the NAc but with some stimuli there is also ΔFosB induction in .

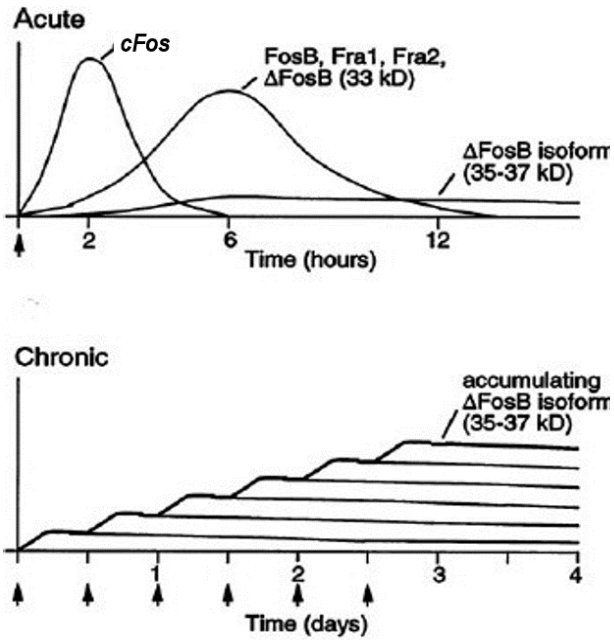


Figure 8 *Top part. Schematic of time courses of the Fos family proteins as obtained by immunoblots in NAc with acute exposure to cocaine. Depicted are cFos which rises quickly and transiently, followed by somewhat more slowly accruing but transient FosB, Fra1, Fra2 and the least stable form of ΔFosB all of which are shown here to have about the same time course. However, as will be seen below, other reports indicate differing time courses for FosB, Fra1, Fra2 and ΔFosB. The modified 35-37 kDa forms of ΔFosB rise more slowly and decay very slowly. Bottom part. With time in days the transients are not apparent with two cocaine exposures per day for 2.5 days but with each stimulus there is a ramp-like increase in the 35-37 kDa forms of ΔFosB. Contributions from successive doses accumulate to give a stair-case type function with decay occurring quite slowly. The original graphic was given in Hope et al. (1994b); the present diagram is based on the adaptation in Nestler et al. (2001).*

D2-type MSN (Nestler, 2015b), as summarized for NAc shell and core and dorsal striatum in Lobo et al. (2013). Furthermore, owing to their great stability, $\Delta FosB^{35}$ and $\Delta FosB^{37}$ have a strong and lasting influence on drug-related behavior which may persist up to months after the end of drug exposure (Nestler, 2004a) thus playing an essential role in addiction. Also, ΔFosB with molecular masses of 35-37 kDa accumulates during chronic stress and due to its extraordinary stability it remains in neurons for many weeks after the termination of stress (Nestler, 2015a).

3.2.1 Timing of mRNA and protein levels

Generally accepted times for the main steps from the commencement of transcription to protein synthesis in eurkaryotes are as follows. Transcription from DNA to mRNA occurs on the order of a few minutes to 20 minutes. Transport of mRNA from nucleus to cytoplasm (ribosomes) takes approximately 10 to 30 minutes but the translation to protein is much faster, occurring within one or a few minutes. Hence protein starts to appear about 30 minutes to 1 hour after transcription starts. In prokaryotes, the transport step is missing so the time delay from transcription to translation is shorter, a figure of 7.5 to 10 minutes being used in a stochastic model of gene expression in Escherichia coli (Gedeon & Bokes, 2012).

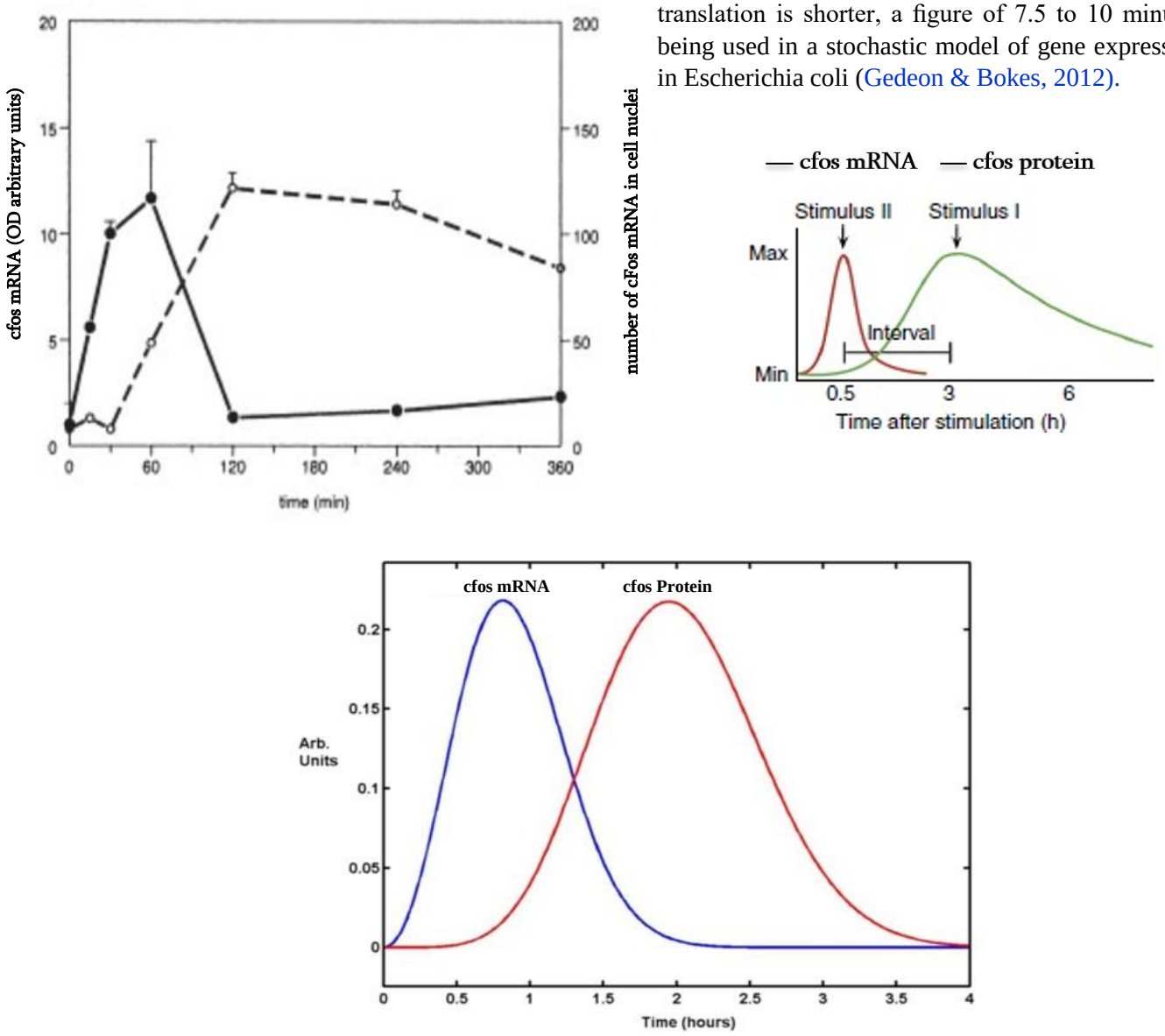


Figure 9 *Top left. mRNA level (solid line) and number of cfos active cells (dashed line) in NAc in response to haloperidol injections in rats. Adapted from Kovács et al. (2001). Top right. cfos mRNA and protein in NAc resulting from sequential stimuli of morphine (mRNA) and foot-shock (protein). Adapted from Xiu et al. (2014). Bottom part. Estimated time courses from various sources (see text) of cfos mRNA and cFos protein approximated by analytical expressions.*

Line drawings which display levels of mRNA and protein are not common. In a study of the expression of c*fos* in response to injections of various antipsychotic drugs in several brain regions, Kovács et al. (2001) showed such graphical results for c*fos* mRNA and for the number of cells exhibiting cFos protein expression. Such data gives an approximate idea of the relative timing of c*fos* mRNA induction and its translation to the protein. The highest levels of cFos protein in response to haloperidol were found in the NAc and CPu. Results for the effects of haloperidol on c*fos* activity in the NAc are shown in the top left part of **Figure 9**. The maximum level of c*fos* mRNA occurs at about 30 minutes after drug administration whereas the maximal protein induction was seen at the two-hour time point. Similar results were reported by Xiu et al. (2014) as reproduced in the middle part of **Figure 9**. These results were obtained in NAc by superimposing results to two stimuli, morphine and foot-shock.

Using experimental results for c*fos* mRNA and protein from various preparations with acute stimuli (Mitchell et al., 1986; Sonnenberg et al., 1989; Winston et al., 1990; Hope et al., 1994b; Chen et al., 1995), an estimate was made of their approximate time courses. These have been fitted by the two expressions with t in hours, firstly for c*fos* mRNA, with a maximum at 45 minutes

$$C_m(t) = 0.7t^2 \exp(-2(t - 0.2)^2), \quad (1)$$

and secondly for cFos protein with a maximum at 2 hours

$$C_p(t) = 0.05t^5 \exp(-2((t - 0.5)/1.5)^2). \quad (2)$$

4. Jun family

Many other transcription factors influence the production of fos family genes and proteins. This influence, which can be negative or positive, is often mediated through dimers called AP-1 as discussed below. These dimers may be composed of a fos family protein with a protein from another group of IEGs called the jun family whose three main members are cJun, JunB and JunD. The last to be discovered was *jun*D by Ryder (1989) which also has information about the other two members. The molecular masses of the jun family members do not seem to be as well documented as those for fos family. Some representative figures are, in kDa, cJun, 39, 39, 40-44: JunB, 39, 42, 44-46; and JunD, 39, 42 45-46, these data being from Kovary & Bravo (1991), Bamberger et al. (2004) and De Leon et al. (1995). The c*jun* promoter has a different structure from that of c*fos* (Angel & Karin, 1991; Sng et al., 2004). The *jun*B promotor does not have a serum response element but it contains an element that can mediate responses to protein kinase A and protein kinase C (de Groot et al., 1991; Moratalla et al., 1993). Furthermore, early experiments indicated that cJun could positively regulate c*jun* transcription, in contrast to the negative effects of cFos and cJun on c*fos* transcription (Sassone-Corsi et al., 1988).

In quiescent fibroblasts c*jun* and *jun*B are at very low levels whereas *jun*D is at relatively high levels but serum stimulation leads to large increases in the expression of c*jun* and *jun*B but only a small increase in that of *jun*D (Ryseck & Bravo, 1991).

The abundance of jun family proteins and mRNAs varies greatly across brain regions and must depend on the history of activity. In rat, cJun protein was found at a high level in the dentate nucleus (Hughes et al., 1992). c*jun* mRNA is expressed weakly in cerebral cortex but more strongly in parts of the hippocampus (Mellstrom et al., 1991). The same study reported that *jun*B and *jun*D mRNAs were expressed at high levels in hippocampus striatum, thalamus, cortex, amygdala, and cerebellum.

Schwarzchild et al. (1997) found that glutamate induced both c*fos* and c*jun* mRNA in cultured striatal neurons, though c*fos* is induced much more strongly, as shown here in **Figure 10**, whereas dopamine and the cAMP agent forskolin induced c*fos* but not c*jun*.

In parallel with the results for fibroblasts, in brain, acute application of dopamine-releasing stimulants such as amphetamine and cocaine leads in striatum to the strong expression of *jun*B and to a lesser extent c*jun* (Persico et al., 1993; Cole et al., 1992; Moratalla et al., 1993; Konradi et at., 1996). Similar results were obtained in nucleus accumbens with caffeine by Svenningson et al. (1995).

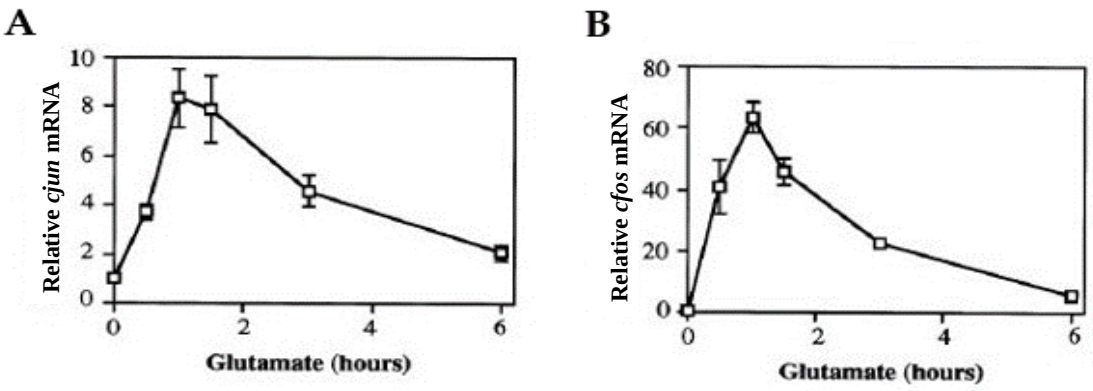


Figure 10 *The induction of cfos and cjun by glutamate. Adapted from Schwarzchild et al. (1997).*

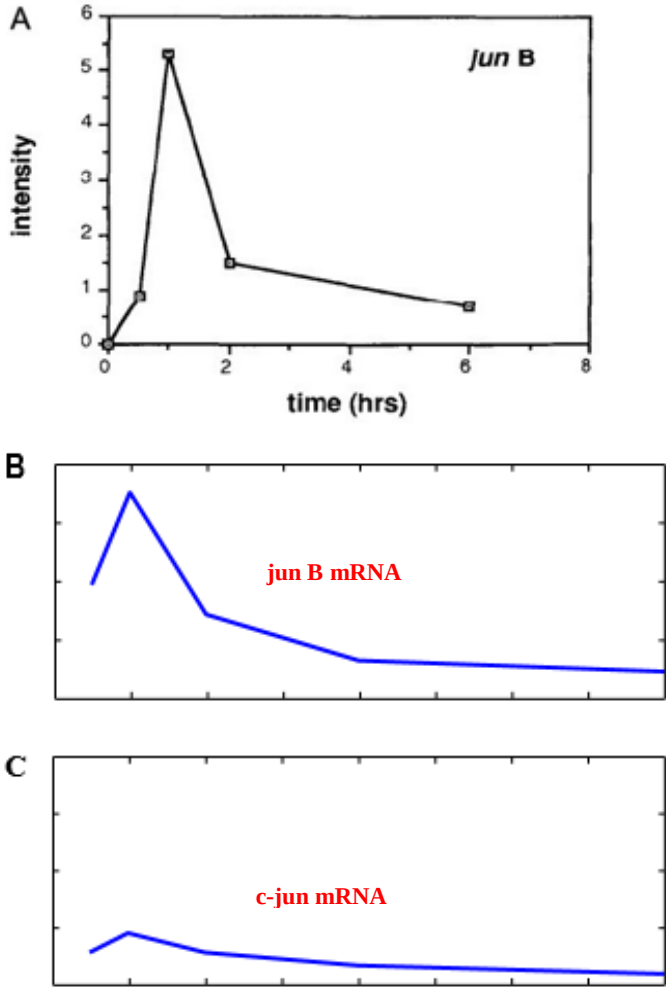


Figure 11 ***A****. junB mRNA levels versus time with cocaine in rat striatum, from Moratalla et al. (1993).* ***B****. junB and cjun mRNA measured in rat nucleus accumbens with caffeine (100 mg/kg). Based on data in Svenninson et al. (1995).*

Figure 11A shows the time course of *jun*B mRNA in the study of Moratalla et al. (1993) and **Figure 11B** depicts the results of Svenninson et al. (1995). Some idea of the relative strengths of c*fos* and *jun*B is obtainable from the data of Persico et al. (1993) for rat striatum where acute amphetamine resulted at 1 hour in c*fos* increasing by about 380%, *jun*B by 425% and c*jun* by 94%.

5. Discussion

The induction of genes by neuronal activity is fundamental to such processes as long term potentiation and depression and addiction due to stimulants like cocaine and amphetamines, which result in increased stimulation of dopamine receptors of such cells as the medium spiny neurons of the striatum, particularly the nucleus accumbens. Intense research over the last 25 years has revealed details of the complex biochemical sequences of reactions leading to transcription of many genes. Similar quests have been made to unravel the details of genetic changes involved in many pathologies such as Alzheimer's disease and several other psychiatric disorders–see, for example, the review by Yap & Greenberg (2018). The present article reviews some of the quantitative aspects of such neurogenomical processes. Recent reviews pertinent to c*fos* transcription and the transcription factors involved in cocaine addiction are contained in Lara-Aparicio et al. (2022), Cruz-Mendoza et al. (2022), Dalhäusser, Rössler & Thiel (2022) and Teague & Nestler (2022). Further analysis of the complex circuits involved and their modeling will be analyzed in detail in future articles.

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Abbreviations

AP, action potential; AP-1, activator protein-1; ATF, activating transcription factor; AMPA(R), α- amino-3-hydroxyl-5-methyl-4-isoxazole-propionate type (receptor); BDNF, brain-derived neurotrophic factor; CK2, casein kinase 2; PKA, protein kinase A; CaM, calmodulin; CaMKII, Ca2+/calmodulindependent protein kinase II; CaN, calcineurin, also called protein phosphatase 2B (PP2B, PPP3); CBP, CREB binding protein; CPu, caudate-putamen; CRE, cAMP response element; CREB, cyclic AMP response element-binding protein; DARPP-32, dopamine- and cAMP-regulated 32 kDa phosphoprotein; DREAM, downstream repressor element antagonist modulator: DS, dorsal striatum; DSE, dyad symmetry element (part of SRE); DUSP, dual-specificity phosphatase; EGF, epidermal growth factor; Elk1 or Elk-1, member of a ternary complex factor (TCF) subgroup of the family of ETS (E-twenty-six) domain transcription factors; EPSP, excitatory post-synaptic potential; ERK, extracellular signal-regulated kinase; FRA, Fos-related antigen; g9A, EHMT2, euchromatic histonelysine N-methyltransferase (Ehmt2); GAPDH, glyceraldehyde- 3-phosphate dehydrogenase; H4, acore histone that may be covalently modified; H3K9me2, H3 lysine 9 modified with covalency 2; HDAC1, histone deacetylase 1; ICER, inducible cAMP early repressor; IEG, immediate early gene; K, abbreviation for lysine; kDa, kiloDalton; LC, locus coeruleus; MAPK, mitogen-activated proteininase(s); MEK, MAPKK, MAP kinase kinase; mRNA, messenger RNA; MSK1, mitogen and stress-activated protein kinase; MSN, medium spiny neuron; NAc, nucleus accumbens; NMDA(R), N-methyl-D-aspartate type (receptor); pCREB, phosphorylated CREB; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PKA, protein kinase A; PP1, PP2A, protein phospatase 1, 2A; PRC2, Polycomb Repressive Complex 2; PTB1, polypyrimidine tract binding protein; Ras-GRF1, Ras guanine nucleotide exchange factor-1; RSK, ribosomal subunit protein S6 kinase; S, abbreviation for serine; SIE, sis-inducible element; SIRT, silent information regulator of transcription; SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulata; SRE, serum response element; SRF, serum response factor; STEP, striatal-enriched tyrosine phosphatase (Ptpn5); SWI/SNF, mating switching and sucrose non-fermenting complex; T, abbreviation for threonine; TrkB, tyrosine receptor kinase B; U2AF, splicing factor; VTA, ventral tegmental area; Y, abbreviation for tyrosine.

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