Role of Monoamine Systems in Activation of *zif268* by Cocaine

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Rapid activation of transcription factor genes is thought to play a key role in stimulus-induced neuronal plasticity. To help understand the genomic response that may underlie long-term effects of cocaine and amphetamine, we have investigated the effect of these agents on *Zif268*, a transcription regulatory factor that is expressed at high levels in brain neurons. Like c-*fos*, *zif268* is markedly activated in striatum by cocaine and amphetamine. This response appears to involve the dopamine system, since it is abolished by SCH23390, a selective D_1 dopamine receptor antagonist, or by 6-hydroxydopamine lesions. To assess the role of other monoamine systems in regulating the expression of these transcription factors, we have examined the effects of selective monoamine uptake blockers as well as agents that lesion the norepinephrine and serotonin systems. These studies indicate that, in addition to the dopamine system, the norepinephrine and serotonin systems also play prominent roles in the activation of *zif268* and c-*fos* by cocaine and amphetamine.

Key Words: serotonin, norepinephrine, immediate early gene, c-*fos*, amphetamine, striatum

Recent studies have demonstrated that physiological and pharmacological stimulation can elicit rapid and transient increases in the neuronal expression of several transcription regulatory factors (Morgan and Curran 1989; Sheng and Greenberg 1990; He and Rosenfeld 1991). By binding to regulatory regions of DNA in a sequence-specific manner, these factors are thought to play a key role in orchestrating alterations in gene expression underlying stimulus-induced neuronal plasticity (Goelet et al 1986; Morgan et al 1987; Sheng and Greenberg 1990). The intriguing possibility that this type of genomic response may underlie the delayed or long-term effects of psychotropic agents in the brain has generated considerable interest in this area of research among neuropharmacologists.

Investigations into this process in cultured cells indicate that neurotransmitter stimulation of receptors on the cell surface initiates a signal that is conveyed to the nucleus and triggers increased mRNA synthesis of these rapidly inducible transcription factors. Although the signalling pathways leading from the cell surface to the nucleus are far from completely understood, recent evidence suggest that both the cyclic AMP and calcium second messenger systems are involved in mediating this response (Sheng and Greenberg 1990; Murphy et al 1991a; 1991b). This rapid genomic response in neurons has been found to be quite complex. Initial studies focused on the activation of members of the Fos/Jun leucine zipper family of transcription factors. Members of other families of transcription factors are activated as well. For example, several factors belonging to the zinc finger or *zif* family of transcription factors, including *zif268* (Christy et al 1988) also called *NGFI-A* (Milbrandt 1987), or egr-1 (Sukhatme et al 1988), *krox-20* (Chavrier et al 1988) and *NGFI-C* (Crosby et al 1991) are also induced by neuronal stimulation (Cole et al 1989; Wisden et al 1990; Bhat et al 1992; Crosby et al 1992).

The differential expression of these transcription factors is thought to play a key role in determining the specific patterns of target gene expression elicited in response to a given stimulus. For example, all three members of the *zif*

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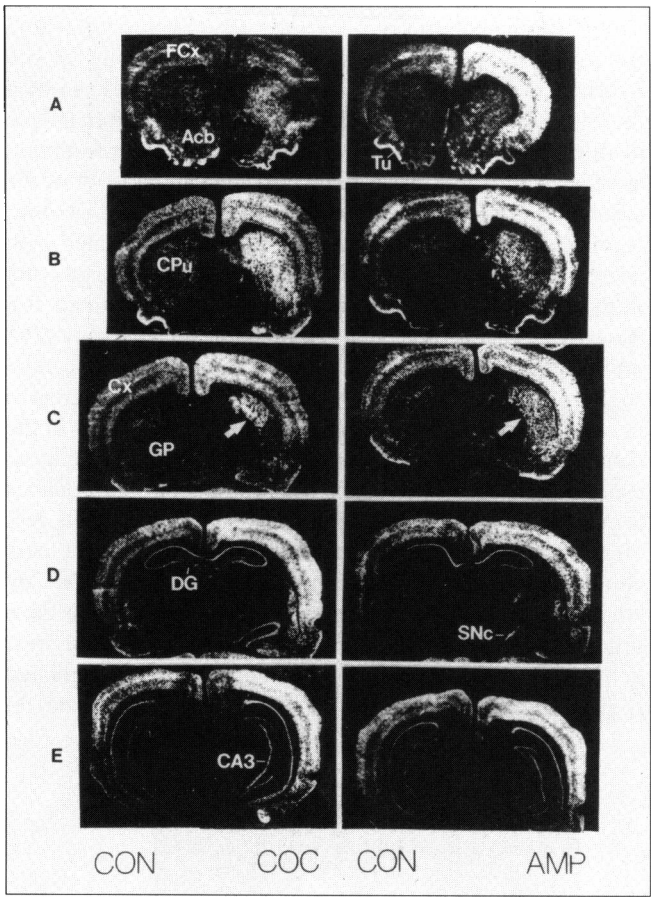

Fig. 1: Localization of *zif268* mRNA in brain after cocaine and amphetamine. Autoradiograms of coronal sections taken at various brain levels (A-E), hybridized with *zif268* antisense riboprobe. Animals treated with either cocaine (COC) (15 mg/kg) or amphetamine (AMP) (5 mg/kg) were sacrificed 30 min after i.p. administration of these drugs and compared with control (CON) rats. Brains were rapidly removed, placed on ice and cut sagitally on the midline. These hemibrains were then aligned with hemi-brains obtained from control animals, embedded together and processed for *in situ* hybridization as described previously (Bhat et al 1992a). FCx = frontal cortex, Tu = olfactory tubercle, Acb = nucleus accumbens, CPu - caudate-putamen, GP = globus pallidus, DG = dentate gyrus, SNc=-substantia nigra pars compacta, CA_3 = field of hippocampus.

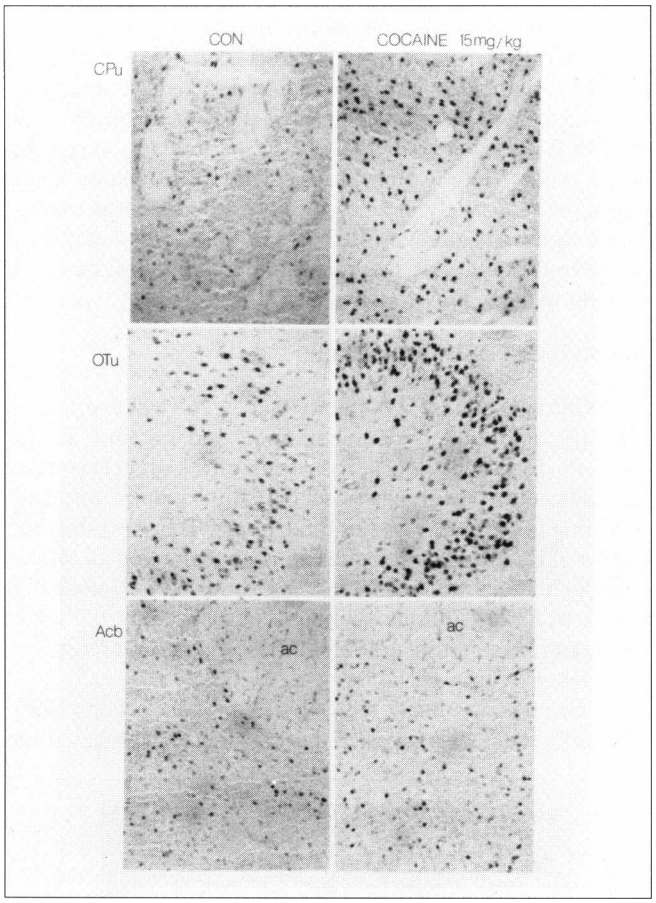

Fig. 2: Localization of *Zif268* protein in brain after cocaine. Immunohistochemical staining of *Zif268* protein as described previously (Worley et al 1991) in caudate-putamen (CPu), olfactory tubercle (OTu), and nucleus accumbens (Acb), two hours after i.p. administration of 15 mg/kg cocaine (right panel) compared with control (CON) rats (left panel).

family are induced by seizure activity in dentate granule cells of the hippocampus (Saffen et al 1988; Bhat et al 1992; Crosby et al 1992). However, *krox-20* is expressed during early development in the hindbrain in a segmental pattern, whereas *zif268* and *NGFI-C* are not (Wilkinson et al 1989; Charvier et al 1990). Conversely, *zif268* and *NGFI-C*, but not *krox-20*, are induced in PC12 cells by nerve growth factor stimulation (Joseph et al 1988).

Several recent studies have found that the dopamine (DA) system plays a major role in the regulation of c-*fos* in striatal neurons (Robertson et al 1989a; 1989b; Robertson et al 1990; Dragunow et al 1990; Miller 1990; Graybiel et al 1990; Young et al 1991; Robertson and Fibiger 1992). These findings have generated interest in determining: 1. whether or not other transcription factors are also induced by dopaminergic agents; and 2. whether or not other monoamine systems also strongly influence expression of transcription factors in brain neurons. In recent years, our laboratory has focused on studying the regulation of the zinc finger family of transcription factors in the brain, especially *zif268*, a member of this family that is expressed at high levels in brain (Worley et al 1990;

Worley et al 1991). *Zif268* has attracted attention because it is selectively induced by synaptic NMDA receptor stimulation that elicits long-term potentiation of the perforant path input to the dentate granule cells of the hippocampus (Cole et al 1989; Wisden et al 1990). Also, particularly intriguing is the recent finding that the atypical antipsychotic agent clozapine selectively induces *zif268* (Robertson and Fibiger 1992; Nguyen et al 1992). In this review, we will summarize our recent studies of the role of monoamine systems in regulating the expression of *zif268*.

Activation of *zif268* by cocaine

In initial studies, we found that *zif268*, like c-*fos*, is robustly activated by amphetamine and cocaine in the striatum (Cole et al 1992). The rise in mRNA levels is rapid and transient, peaking between 30 min and 60 min and returning to basal levels after three hours. To assess the time course of *Zif268* protein expression, we employed an immunohistochemical approach. In these studies, we found that increased *Zif268* immunostaining is apparent approximately two hours after administration of these agents and returns to basal levels within six hours.

Detailed anatomical studies by Graybiel's group (1990; Moratalla et al 1992) revealed that cocaine and amphetamine elicit different patterns of c-*fos* and *zif268* expression within the striosomal compartments of the striatum. Using *in situ* hybridization and immunohistochemistry, we have examined the expression of *zif268* and found that these agents induce distinct anatomical patterns of expression in other forebrain areas as well (see Figs. 1 and 2). At the caudal level of the striatum, *zif268* activation by cocaine (15 mg/kg, i.p. 30 min) is prominent in the dorsal caudate-putamen (indicated with an arrow on Figs. 1 and 2), with the ventral portion displaying little response. In contrast, amphetamine administered at a dose (5 mg/kg, i.p.) that elicits comparable increases in *zif268* mRNA produces a uniform increase throughout the caudal striatum. Neither cocaine nor amphetamine elicits increases in *zif268* in the adjacent globus pallidus. Differences in the pattern of *zif268* activation are also apparent in the cortex, especially in the frontal cortex, where amphetamine produces a marked increase in *zif268* mRNA, but cocaine has less effect. Careful examination of the substantia nigra pars compacta reveals an intense increase in *zif268* mRNA by amphetamine. In contrast, cocaine and amphetamine have little, if any, effect on *zif268* in the ventral tegmental area. Within the hippocampus, *zif268* appears to be activated slightly in the CA_3 field by both agents. By comparison, no

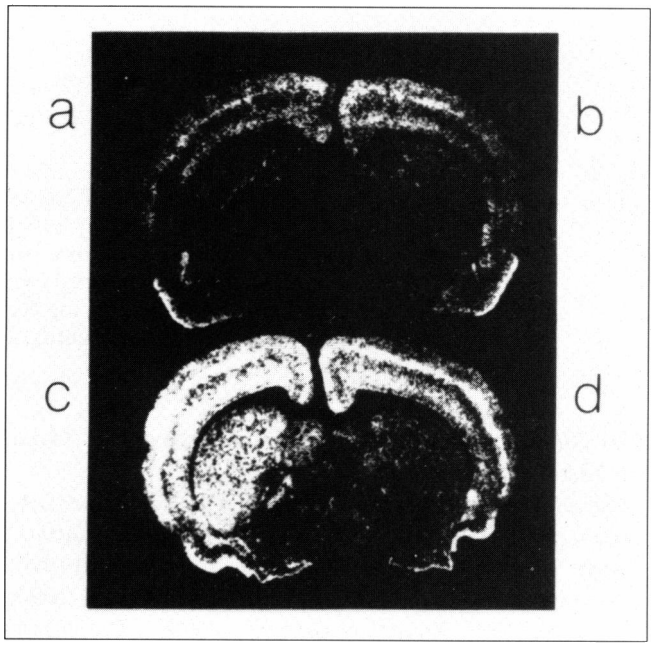

Fig. 3: Blockade of amphetamine's activation of *zif268* by a D_1 receptor antagonist. *In situ* hybridization autoradiograms of paired hemibrains showing effect of 0.5 mg/kg of SCH23390 administered i.p., 15 min prior to an i.p. injection of 5 mg/kg amphetamine. Rats were sacrificed 30 min after injection of amphetamine. (a) control (b) SCH23390 (c) amphetamine (d) SCH23390 + amphetamine.

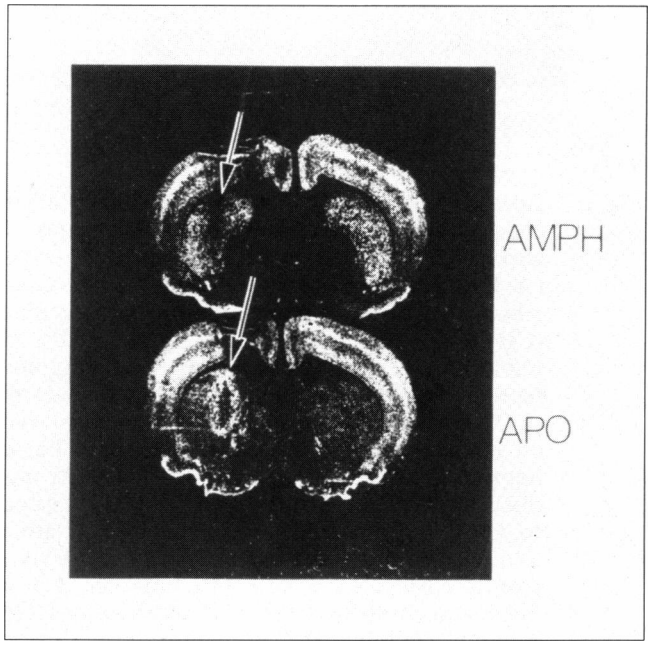

Fig. 4: Effect of 6OHDA lesion on *zif268*'s response to amphetamine and apomorphine. Rats were stereotaxically injected with 8 μg 6OHDA in the striatum (Cole et al 1992). Ten days later they were injected (i.p.) with either 2 mg/kg apomorphine (bottom) or 5 mg/kg amphetamine (top) and sacrificed 30 min after the latter injection. Coronal sections were taken at the site of the lesions and hybridized with *zif268* antisense riboprobe.

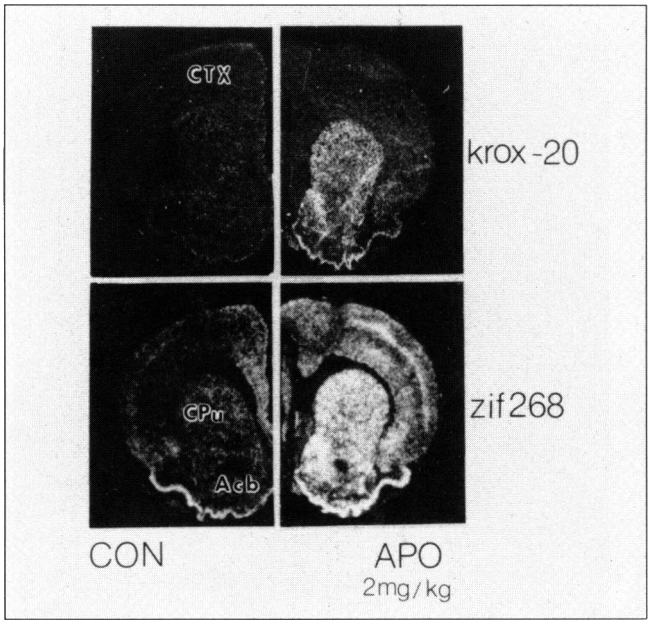

Fig. 5. Activation of *krox-20* and *zif268* by apomorphine. *In situ* autoradiograms of coronal sections of hemibrains 30 min after apomorphine (APO) or vehicle injection. All rats were pre-treated with reserpine 5 mg/kg i.p. 18 hours and three hours prior to sacrifice and then with APO or vehicle 30 min prior to sacrifice. Left brain hemispheres (A,C) from vehicle injected control (CON); right brain hemispheres (B,D) are from rats injected with APO 2 mg/kg i.p. CTX= cortex; Acb= nucleus accumbens; Cpu=caudate-putamen; OTu= olfactory tubercle.

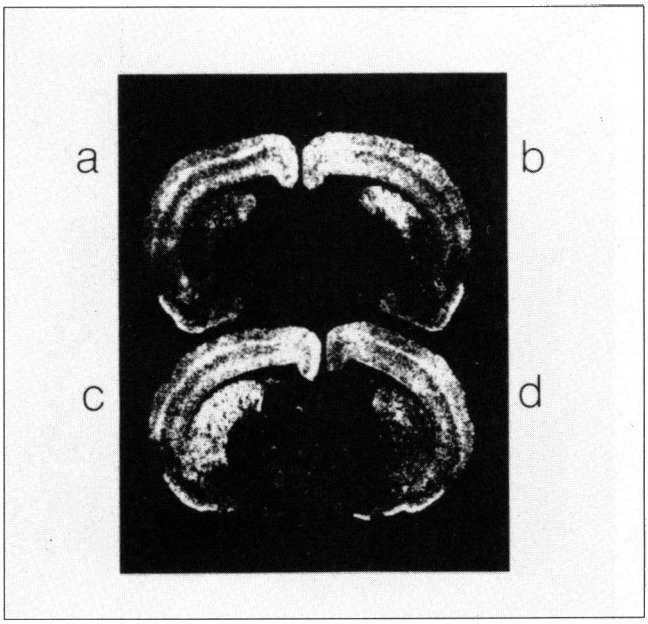

Fig. 6. Effect of co-administration of DA and 5-HT uptake inhibitors on *zif268*. *In situ* autoradiograms showing effect of (a) mazindol 2 mg/kg (top left) or (b) mazindol 2 mg/kg + fluoxetine 10 mg/kg (top right). Bottom: paired hemibrains of either (c) fenfluramine 5 mg/kg + mazindol 2 mg/kg (bottom left) or (d) fenfluramine 5 mg/kg (bottom right). Fluoxetine (10 mg/kg) had no effect when administered alone (data not shown). Rats were sacrificed 30 min after administration of drugs.

effect is observed in the dentate gyrus region of the hippocampus. The basis for the distinct patterns of activation induced by these drugs is unclear, but may reflect known differences in their effects on monoamine systems. For example, amphetamine releases monoamines, while cocaine appears to act primarily by blocking monoamine re-uptake. Cocaine may therefore be effective only in areas with substantial basal release of monoamine transmitters.

Pharmacological analysis of the activation of *zif268* by cocaine and amphetamine in striatum has revealed a selective role for D_1 receptors, similar to that displayed by c-*fos*, as these responses are totally blocked by the D_1 receptor antagonist SCH23390 (Cole et al 1992) (see Fig. 3). Attempts to explore the effects of direct DA receptor agonists have uncovered a curious aspect of the pharmacology of this response; although indirect agents, such as amphetamine and cocaine, induced robust increases in *zif268* expression, direct agonists, such as apomorphine, were ineffective. Since amphetamine and cocaine exert prominent effects on other monoamine systems, we conducted additional studies to examine whether or not the activation of *zif268* by these drugs was mediated by the DA system. Lesioning the DA system with 6-hydroxydopamine (6-OHDA) blocked induction of *zif268* by amphetamine and cocaine, confirming the involvement of the DA system. Interestingly, in 6-OHDA lesioned animals, apomorphine was effective at inducing *zif268* (see Fig. 4). Following reserpine pre-treatment, apomorphine also became effective at activating *zif268*. Thus, reduced dopamine tone, rather than denervation per se, appears to be sufficient to induce responsiveness to apomorphine (Cole et al 1992). Using this reserpine paradigm, we found that apomorphine's activation of *zif268* is blocked by SCH23390 but not by D_2 receptor antagonists. Furthermore, the selective D_1 receptor agonist SKF38393, but not the D_2 agonist LY171555, stimulates the expression of *zif268*. Similar pharmacological profiles were observed when we examined members of the Fos/Jun leucine zipper family including *Fos*B, c-*jun* and *jun*-B, as well as a member of the zinc finger family of transcription factors, *krox-20* (Bhat et al 1992) (see Fig. 5).

These studies demonstrate that the D_1 receptor plays a key role in regulating the coordinate expression of multiple transcription factors in striatum. Since the D_1 DA receptor is coupled to adenylate cyclase (Kebabian and Calne 1979) and

the cyclic AMP system has been implicated in activation of c-*fos* in *in vitro* systems (Sheng and Greenberg 1990), this second messenger system may mediate the genomic response triggered by activation of the DA system. Since these transcription factors are thought to orchestrate long-term changes in gene expression, these findings indicate that D_1 DA receptors may play a special role in mediating long-lasting or delayed effects of this transmitter on neuronal gene expression.

Role of serotonin and norepinephrine systems in the activation of *fos* and *zif268* by cocaine

The results described above reveal a discrepancy, in naive animals, in the response of *zif268* to agents that act indirectly, such as cocaine and amphetamine, and those which act directly, such as apomorphine. Therefore, we explored the possibility that this reflected the ability of cocaine and amphetamine to act on multiple monoamine systems, whereas apomorphine is a selective DA receptor agonist. In other words, stimulation of D_1 receptors may be necessary but not sufficient to activate transcription factor genes. In this set of studies, we examined whether or not cocaine's induction of *zif268* involved serotonin (5-HT) and norepinephrine (NE) systems, by lesioning them with p-chloroamphetamine (PCA) (Dewar et al 1992) and DSP4 (Jonsson et al 1981), respectively. When naive control rats were compared with rats treated with either PCA or DSP4, a reduction of the basal expression of *zif268* in the striatum and cortex was observed; this finding suggests that each of these monoamines is involved in driving the expression of this gene under normal physiological conditions (Bhat and Baraban, unpublished data). After undergoing lesions of the 5-HT or NE systems with PCA or DSP4 treatment, respectively, rats were challenged with an injection of either cocaine or amphetamine. Activation of *zif268* in the striatum by cocaine or amphetamine is attenuated after removal of the 5-HT input, but not after NE lesions (Bhat and Baraban 1992). c-*fos* protein expression, assessed immunohistochemically, displays the same profile. These findings suggest that effects of cocaine and amphetamine on both DA and 5-HT systems may mediate their activation of transcription factor genes.

A key role of the 5-HT system in mediating this genomic response is also supported by studies using selective monoamine uptake blockers (Bhat and Baraban 1992). While selective 5-HT uptake inhibitors, such as fluoxetine and citalopram, do not affect *zif268* mRNA levels in the striatum by themselves, these agents enhance the modest activation of *zif268* produced by mazindol, a selective inhibitor of DA and NE uptake (see Fig. 6). In contrast, the administration of desipramine, a selective NE uptake inhibitor, with fluoxetine does not induce *zif268* or c-*fos*. These studies indicate that signals derived from both 5-HT and DA systems can act synergistically to trigger genetic programs orchestrated by these transcription factors. Further studies with 5-HT receptor antagonists should help identify which of the rapidly growing family of 5-HT receptor subtypes is linked to activation of these transcription factor genes.

Chronic exposure to cocaine suppresses basal expression of *zif268*

In recent studies, we and others have examined the effects of repeated exposure to cocaine on *zif268* expression (Bhat et al, in press; Ennulat et al 1991). In contrast to the rapid and transient activation of *zif268* induced by a single injection of cocaine, long-term administration of this agent suppresses basal *zif268* mRNA levels for 24 to 48 hours after the last dose of cocaine. Our findings are consistent with the preliminary studies by Ennulat et al (1991), in which chronic cocaine infusion dramatically suppressed *zif268* mRNA in the striatum, assessed by Northern blot analysis. Our studies suggest that the suppressive effects on this transcription factor gene are seen throughout the neocortex. Since NE or 5-HT depletion elicits a similar reduction in *zif268* expression in the cortex, this suppression produced by cocaine may reflect its ability to disrupt activity in NE or 5-HT input to the cortex.

Summary

These studies suggest that, in addition to the DA system, other monoamine systems participate in regulating transcription factor expression in the brain. Detailed analysis of the rapid genomic response induced by cocaine indicates that the ability of this drug to block uptake of both 5-HT and DA may underlie its robust activation of transcription factor genes in the striatum. These studies also suggest that the prominent basal levels of *zif268* expressed in the cortex are driven, in part, by the NE and 5-HT input. Brief bursts of activity in the NE projection to the cortex, emanating from the locus coeruleus, are thought to alert this structure to environmental stimuli (Aston-Jones and Bloom 1981; Foote et al 1983). Perhaps the low level of tonic firing activity displayed by NE neurons in the locus coeruleus (Jacobs 1987) and 5-HT cells in the dorsal raphe (Aghajanian and Rasumssen 1989) exert an important influence on neuronal gene expression by maintaining high basal levels of *zif268*.

Although the target genes regulated by *zif268* have not yet been identified, it appears likely that this transcription factor plays a major role in coupling incoming synaptic stimuli to alterations in gene expression. Evidence described above that the 5-HT and NE systems play a key role in regulating expression of *zif268* raises the possibility that the long-term effects of agents, such as antidepressants, antipsychotics and drugs of abuse, thought to act via these monoamine systems, may involve changes in gene expression mediated by *zif268* or similarly regulated transcription factors.

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