Amphetamine and cocaine induce different patterns of c-fos mRNA expression in the striatum and subthalamic nucleus depending on environmental context

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Abstract

In the dorsal striatum, there are two major populations of medium spiny projection neurons. One population is positive for dynorphin mRNA (DYN+), and these cells project preferentially to the substantia nigra, forming the so-called ‘direct pathway’. A second population is positive for enkephalin mRNA (ENK+), and these cells influence the substantia nigra indirectly, via the globus pallidus and subthalamic nucleus. Psychostimulant drugs, such as amphetamine and cocaine, are reported to induce immediate early genes (IEGs) in only one subpopulation of dorsal striatal projection neurons, DYN+ cells. However, this apparent selectivity appears to be a function of environmental context. We found that when given in the animal's home cage, amphetamine and cocaine increased expression of the IEG, c-fos, almost exclusively in DYN+ cells. However, when given in a novel environment, amphetamine and cocaine increased c-fos mRNA in both DYN+ and ENK+ cells. Furthermore, amphetamine and cocaine increased c-fos mRNA expression in the subthalamic nucleus when administered in the novel environment, but not when given at home. We conclude that the neural circuitry engaged by psychostimulant drugs, and their ability to induce specific patterns of gene expression, are determined by the environmental context in which they are experienced. This may be related to the ability of environmental novelty to facilitate psychostimulant drug-induced neuroplasticity.

Introduction

Psychostimulant drugs, such as amphetamine and cocaine, induce the expression of immediate early genes (IEGs) in neurons throughout the striatal complex (Graybiel et al., 1990; Young et al., 1991; Berke et al., 1998). This may reflect their ability to engage striatal circuitry (Dragunow & Faull, 1989), and also may be indicative of an initial step in the development of cellular adaptations underlying drug experience-dependent plasticity (Morgan & Curran, 1991; Nestler et al., 1993). There are two neurochemically distinct populations of medium spiny projection neurons in the striatum (Albin et al., 1989; Alexander & Crutcher, 1990; Gerfen et al., 1990), and there have been many studies designed to delineate which population expresses IEGs following psychostimulant drug administration. There is almost complete consensus that amphetamine and cocaine induce IEG expression only in striatal neurons that are positive for prodynorphin mRNA (dynorphin+, DYN+, or enkephalin-negative, ENK−, neurons). These neurons project preferentially to the substantia nigra, forming the so-called ‘direct’ pathway. Amphetamine and cocaine reportedly fail to induce IEGs in striatal neurons that are positive for proenkephalin mRNA (ENK+ neurons), which project preferentially to the pallidum and subthalamic nucleus (STN), forming the so-called ‘indirect’ pathway (Berretta et al., 1992, 1993; Cenci et al., 1992a, b; Johansson et al., 1994; Ruskin & Marshall, 1994; Kosofsky et al., 1995; Moratalla et al., 1996; Berke et al., 1998; Harlan & Garcia, 1998).

We have found, however, that the ability of amphetamine to induce the IEG, c-fos, is modulated powerfully by the environmental context in which it is experienced. In the striatum, for example, amphetamine induces much higher levels of c-fos mRNA when it is given in a novel environment, relative to when it is given in the home cage (Badiani et al., 1998). Also, consistent with the literature, we found that when amphetamine was given at home it induced c-fos mRNA expression in cells positive for dopamine (DA) D1 receptor mRNA (the DYN+ cells), but not in cells positive for DA D2 receptor mRNA (the ENK+ cells). In contrast, when we gave amphetamine in a novel environment it induced c-fos mRNA expression in both D1 and D2 mRNA+ cells (Badiani et al., 1999). This suggests that the context in which amphetamine is experienced may not only modulate the magnitude of IEG expression, but may determine which populations of striatal cells are engaged.

To further address this issue we have characterized the ability of amphetamine to induce the IEG, c-fos, in neurochemically distinct striatal cell populations, as a function of environmental context, but using probes for either proenkephalin mRNA (to identify the ENK+ cell population) or prodynorphin mRNA (to identify the ENK− cell population). In addition, in our earlier experiments we quantified c-fos expression in the intact hemisphere of rats that had a unilateral 6-hydroxydopamine (6-OHDA) lesion (Badiani et al., 1998, 1999). This is potentially problematic because a unilateral 6-OHDA lesion
may alter neurotransmission even in the intact hemisphere (e.g. Robinson, 1991), and therefore, the present study was conducted using neurologically intact rats. Also, in our previous experiment we only studied amphetamine, and in the present experiment we sought to determine if environmental context has a similar effect on c-fos expression evoked by cocaine. Finally, to further explore the involvement of the ‘indirect’ pathway, we also examined c-fos expression in the STN, one component of this circuit.

Materials and methods

Subjects

Fifty-six male Sprague–Dawley rats (Harlan, Indianapolis, IN, USA) weighing 200–250 g were housed initially in stainless steel hanging cages in a temperature- and humidity-controlled colony room. The rats were kept on a 14 : 10 h light : dark cycle (lights on at 07.00 h) and were given food and water ad libitum. The animals were kept in the colony room for 7 days before any experimental manipulation. The experimental procedures were approved by the University of Michigan Committee on the Use and Care of Animals.

Testing procedures

Rats were assigned to one of seven groups. Animals in three groups were housed singly in 40.6 cm × 27.9 cm × 19.1 cm (white plastic tubs), where they immediately received saline (novelty group, n = 9) or 15 mg/kg of cocaine (home/cocaine group, n = 9) in their home cages, whereas animals in the other three groups were transferred from their home cages to novel test cages (white plastic tubs), where they immediately received saline (novelty group, n = 9), 1.5 mg/kg of amphetamine (home/amphetamine group, n = 9) or 15 mg/kg of cocaine (novel/cocaine group, n = 9) in their home cages. Thus, three groups were administered saline (home/saline group, n = 5), 1.5 mg/kg of amphetamine (home/amphetamine group, n = 9) or 15 mg/kg of cocaine (home/cocaine group, n = 9) in their home cages, whereas animals in the other three groups were transferred from their home cages to novel test cages (white plastic tubs), where they immediately received saline (novelty group, n = 9), 1.5 mg/kg of amphetamine (novel/amphetamine group, n = 11) or 15 mg/kg of cocaine (novel/cocaine group, n = 9). Note that all animals received their injections in physically identical cages, but for some animals this was home and for others it was a novel environment. In addition, a seventh group was housed in the white plastic tubs but received no injections (un-treated group, n = 4).

Drugs

D-amphetamine sulphate (1.5 mg/mL) and cocaine HCl (15 mg/mL) were dissolved in 0.9% saline. All drug weights refer to the weight of the salts. Drug solutions were administered by i.p. injection (1 mL/kg) and control treatments consisted of saline.

In situ hybridization methods

Fifty minutes following drug treatments, the rats were decapitated, their brains were removed and immediately frozen in isopentane (−40 to −50 °C), and then stored in a −70 °C freezer. Coronal brain sections (10 μm) were cut using a cryostat. Brain sections were taken at the level of the dorsal striatum and the STN (at approximately 0.8 mm posterior and 4 mm posterior to bregma, respectively), thaw-mounted on slides coated with polylysine and stored at −70 °C until processing for in situ hybridization. This level of the dorsal striatum was chosen because it is where we have previously found the largest effect of environmental context on amphetamine-induced c-fos expression (Badiani et al., 1998).

The single in situ hybridization method was adapted from that described by Cullinan et al. (1995) and the double in situ hybridization method from that described by Curran & Watson (1995). Briefly, brain sections were fixed in 4% paraformaldehyde. Sections containing the STN were processed for single in situ hybridization using 35S-UTP and CTP-labelled riboprobes complementary to c-fos (680-mer; courtesy of Dr T. Curran, St Jude Children’s Research Hospital, Memphis, TN, USA). Sections

FIG. 1. The expression of c-fos mRNA in the dorsal striatum of rats given cocaine or amphetamine at home, or in a novel environment, or given saline (t = a novel environment. The illustrations to the right of each panel contain stippled regions that indicate the area of the dorsal striatum that was quantified. (A) The mean (± SEM) number of cells positive for c-fos mRNA as a function of drug and environment. The mean (± SEM) for the control group was 0.22 ± 0.15, and this number was subtracted from the value for each animal in all experimental groups. Thus, the mean of the control group is represented by a value of zero, and all values greater than zero indicate significant expression. All groups showed greater expression than the control group (one-sample t-tests; novel/saline, t = 7.19, P < 0.0001; home/cocaine, t = 2.79, P < 0.02; novel/cocaine, t = 8.34, P < 0.0001; home/amphetamine, t = 4.84, P < 0.002; novel/amphetamine, t = 6.14, P < 0.0003). Animals given cocaine or amphetamine in the novel environment showed higher levels of expression than animals treated at home (novel/cocaine vs. home/cocaine, t = 4.86, P < 0.0001; novel/amphetamine vs. home/amphetamine, t = 2.97, P < 0.0009). Both the novel/cocaine and novel/amphetamine groups differed from the saline group (t = 2.68–5.52, P < 0.02). (B) The mean (± SEM) number of cells positive for c-fos mRNA that were also positive for either dynorphin (DYN) mRNA or enkephalin (ENK) mRNA, as a function of drug and environment. In the control group, no ENK+ cells were positive for c-fos mRNA, and only 0.22 ± 0.15 DYN+ cells were positive for c-fos mRNA. In all groups, there was an increase in the number DYN+ cells that expressed c-fos mRNA, relative to the control group (novel/saline, t = 3.5, P < 0.009; home/cocaine, t = 3.1, P < 0.02; novel/cocaine, t = 7.95, P < 0.0001; home/amphetamine, t = 4.25, P < 0.003; novel/amphetamine, t = 7.01, P < 0.0001). Also, in all groups except the home/amphetamine group, there was an increase in the number ENK+ cells that expressed c-fos, relative to the control group (novel/saline, t = 3.1, P < 0.015; home/cocaine, t = 2.5, P < 0.038; novel/cocaine, t = 4.05, P < 0.004; home/amphetamine, t = 1.79, P = 0.11; novel/amphetamine, t = 4.31, P < 0.002). There was no effect of environment on the number of DYN+ cells that expressed c-fos mRNA (novel/cocaine vs. home/cocaine, t = 1.91, P = 0.073; novel/amphetamine vs. home/amphetamine, t = 1.53, P = 0.147). In contrast, there was a strong effect of environment on the number of ENK+ cells that expressed c-fos mRNA (novel/cocaine vs. home/cocaine, t = 3.01, P < 0.008; novel/amphetamine vs. home/amphetamine, t = 3.31, P < 0.005). The novel/cocaine and novel/amphetamine groups also had more c-fos/ENK+ cells (t = 2.32–3.34, P < 0.033) and c-fos/DYN+ cells (t = 2.45–4.05, P < 0.026) than the novel/saline group. Asterisks indicate that novel is greater than home.
containing the dorsal striatum were processed for dual in situ hybridization using 35S-UTP and CTP-labelled riboprobes complementary to prodynorphin or proenkephalin (733-mer and 693-mer, respectively; courtesy of Dr J. Douglass, Amgen, Thousand Oaks, CA, USA) and a digoxigenin-UTP-labelled riboprobe complimentary to c-fos (680-mer; courtesy of Dr T. Curran). The only alterations to the published protocol were (i) 1.25 µg of linearized plasmid was used to generate the digoxigenin-UTP-labelled probe, and (ii) sections were incubated in 0.1 M glycine and 0.5% Triton-X 100, pH 2.2, for 10 min at room temperature and later fixed in 0.5% glutaraldehyde. These latter steps were included because they help to decrease the colour background after development of emulsion-dipped slides (Day et al., 1999).

Single-labelled sections were exposed to X-ray film (Kodak Biomax, MR, USA) for approximately 3 days and then dipped in emulsion (NTB2, Kodak) and stored at 4°C. Dipped slides were developed (D-19, Kodak), dehydrated in graded alcohols, cresyl-violet stained, and coverslipped with Permount. Double-labelled sections were dipped in Ilford KD-5 emulsion (Polysciences) and stored at 4°C (= 3 days for enkephalin and 2 weeks for dynorphin). After development (D-19, Kodak), the slides were dehydrated in graded alcohols and coverslipped with Permount.

Quantification
Single-labelled sections were quantified as described previously (Badiani et al., 1998). Briefly, brain images were captured with a CCD camera (TM-745, Pulnix, USA) from X-ray film. Semiquantitative analysis was performed on each brain image using National Institute of Health image software. Pixels were counted when the optical density values were greater than 3.5 SD above background value (background obtained from corpus callosum; macro written by Dr S. Campeau, University of Colorado, Boulder, CO, USA). Data are represented as relative integrated optical density of pixels above background, divided by total area (Badiani et al., 1999). When given at home or in a novel environment, both amphetamine and cocaine induced c-fos mRNA expression in DYN+ cells, and there was no significant effect of environment. In contrast, there was a large effect of environment on c-fos mRNA expression in ENK+ cells. When given at home, both amphetamine and cocaine increased c-fos mRNA expression in very few ENK+ cells, although significantly more than in the control condition.

In summary, when given at home, amphetamine and cocaine induced c-fos mRNA expression in many DYN+ cells, but only in very few ENK+ cells. When given in a novel environment, however, amphetamine and cocaine induced c-fos mRNA expression in approximately equal numbers of DYN+ and ENK+ cells. Indeed, the increase in the total number of cells positive for c-fos mRNA seen when psychostimulants were given in a novel environment, relative to when they were given at home (see Fig. 1A), was largely accounted for by the increase in the number of ENK+ cells expressing c-fos mRNA (compare Fig. 1A and B).

Subthalamic nucleus
Figure 3 shows the effect of environment on amphetamine- and cocaine-induced c-fos mRNA levels in the STN. In the control group, levels of c-fos mRNA were very low and the data were normalized by subtraction of the average level of expression in control group (i.e. control expression equals zero). The doses of amphetamine and cocaine used here did not significantly increase c-fos mRNA expression in the STN when these drugs were administered at home, nor did saline administration in a novel environment. In contrast, when administered in a novel environment, both amphetamine and cocaine significantly increased c-fos mRNA expression in the STN (P < 0.01), and the levels of expression were significantly greater than in the home condition (P < 0.02). Figure 4 provides representative densitograms.

Results
Expression of c-fos mRNA in the dorsal striatum
Figure 1 shows the results from analysis of the dorsal striatum. In the control group the levels of expression were extremely low, and for all graphs the data were normalized by subtracting the mean level of expression in the control group. Therefore, values that are significantly greater than zero represent an increase in c-fos mRNA expression above control. The stippled areas on the illustrations to the right of each graph indicate the portion of the dorsal striatum that was analysed. We focused on this region of the dorsal striatum because it is where we previously found the largest drug–environment interaction (Badiani et al., 1998). Figure 1A shows the mean number of cells expressing c-fos mRNA in the dorsal striatum for each group. The number of c-fos+ cells was increased significantly above control in all groups (all P < 0.05), but there were also significant group differences. The greatest number of c-fos mRNA+ cells was found in animals given amphetamine or cocaine in a novel environment, and these groups differed significantly from all other groups (P < 0.02). Figure 1B shows the mean number of c-fos mRNA+ cells in the dorsal striatum that were also positive for either DYN mRNA or ENK mRNA, for each group. Figure 2 provides illustrations of representative sections processed for dual in situ hybridization histochemistry. When given at home or in a novel environment, both amphetamine and cocaine induced c-fos mRNA expression in DYN+ and ENK+ cells, and there was no significant effect of environment. Like psychostimulant drug treatment at home, saline administered in a novel environment increased c-fos mRNA expression in very few ENK+ cells, although significantly more than in the control condition.

Discussion
We report four major findings. (i) In neurologically intact rats (our previous studies were with rats that had a unilateral 6-OHDA lesion),
both cocaine and amphetamine induced c-fos mRNA expression in significantly more cells in the dorsal striatum when the drugs were administered in a novel environment than when they were administered in the home cage. (ii) When given at home, both amphetamine and cocaine induced c-fos mRNA almost exclusively in striatal cells that were positive for dynorphin mRNA (i.e. the ENK– cell population). (iii) When given in a novel environment, however, amphetamine and cocaine induced c-fos mRNA not only in DYN+ cells, but in approximately equal numbers of ENK+ cells. (iv) Amphetamine and cocaine enhanced c-fos mRNA levels in the STN when they were administered in a novel environment, but not when they were administered at home.

Most researchers have reported that amphetamine and cocaine increase c-fos mRNA or Fos-like immunoreactivity (Fos-IR) almost exclusively in ENK– striatal neurons (Berretta et al., 1992; Cenci et al., 1992a, b; Johansson et al., 1994; Ruskin & Marshall, 1994; Kosofsky et al., 1995; Berke et al., 1998). For example, using immunohistochemistry, Berretta et al. (1992, p.769) reported that in rats given either amphetamine or cocaine ‘Fos-positive nuclei were almost never found in enkephalin-positive neurones. Out of 2500 Fos-positive neurones plotted, only two ... were colocalized with enkephalin’. Similarly, using in situ hybridization, Johansson et al. (1994, p. 845) reported that ‘amphetamine and cocaine raised c-fos mainly in substance P-positive cells, but rarely in enkephalin-positive cells’. Therefore, our finding that amphetamine and cocaine increased c-fos mRNA in many ENK+ cells appears, at first glance, to be inconsistent with the literature. However, to the best of our knowledge, in all previous studies but one, psychostimulants were given in the home cage. For example, in all the studies from the Graybiel laboratory, amphetamine or cocaine was given in the home cage (A. Graybiel, personal communication, 18 November 2000). The one exception is a study by Jaber et al. (1995), who reported that although amphetamine induced Fos-IR predominantly in ENK– cells (77% of Fos+ cells were also substance P+), Fos was also expressed in ENK+ cells (33% of Fos+ cells were ENK+). Indeed, these authors report the highest level of psychostimulant-evoked IEG expression in ENK+ cells in the literature, other than the present study and our earlier study in rats with a unilateral 6-OHDA lesion (Badiani et al., 1999). It is especially important to note, therefore, that Jaber et al. (1995) treated rats in a test cage, not in their home cage.

It thus seems that the apparent selectivity of psychostimulant-induced IEG expression in the striatum may be a function of where drugs were administered. When given in a novel environment, the effect of amphetamine and cocaine on c-fos was not restricted to one population of projection neurons. This raises a number of questions regarding the neurotransmitter systems thought to govern psychostimulant-induced IEG expression in the striatum. The ability of amphetamine and cocaine to induce c-fos in the striatum is widely thought to be DA-dependent. The ability of amphetamine or cocaine to induce c-fos mRNA and Fos-IR in the striatum is decreased by a 6-OHDA lesion (Cenci et al., 1992b; Bhat & Baraban, 1993; Cenci & Bjorklund, 1994; Paul et al., 1995; Ishida et al., 1998), or by the coadministration of D1 antagonists (Graybiel et al., 1990; Berretta et al., 1992; Nguyen et al., 1992; Steiner & Gerfen, 1995; Yoshida et al., 1995; Ishida et al., 1998), as is the expression of other IEGs, including zif/268 and arc (Moratalla et al., 1992; Steiner & Gerfen, 1995; Daunais & McGinty, 1996; Kodama et al., 1998). The effect of D2 antagonists is more mixed, and more difficult to interpret, because D2 antagonists can themselves induce expression of c-fos (Graybiel et al., 1990; Young et al., 1991; Ruskin & Marshall, 1994). Nevertheless, LaHoste et al. (2000) reported recently that the D2 antagonist, L-741,626, but not the D3 antagonist, U99194A, or the D4 antagonist, L-745,870, attenuated amphetamine-stimulated Fos-IR in the striatum. However, all of these studies presumably characterized c-fos expression primarily in ENK– cells, because expression in ENK+ cells has not been studied.

Consistent with the notion that amphetamine-evoked c-fos mRNA expression in ENK– cells is DA-dependent, we found that a 6-OHDA lesion abolishes the ability of amphetamine to increase c-fos mRNA in cells also positive for D1 receptor mRNA (ENK– cells), regardless of environmental context. However, we also found that a 6-OHDA lesion does not reduce c-fos mRNA in striatal neurones positive for D2 receptor mRNA (ENK+ cells) when amphetamine is administered in a novel environment (Badiani et al., 1999). This is an important finding because it is the first to suggest that different neurotransmitter systems are responsible for psychostimulant-evoked increases in c-fos mRNA expression in different striatal projection neurons, and that the induction of c-fos in the ENK+ cell population requires the actions of a neurotransmitter(s) other than DA.

At this point it is pure speculation as to what neurotransmitters are involved in the induction of c-fos in ENK+ cells. Nevertheless, there are reasons to suspect that glutamate may be involved. First, NMDA receptor antagonists decrease amphetamine- and cocaine-evoked expression of a number of IEGs in the striatum (Snyder-Keller, 1991; Ohno et al., 1994; Wang et al., 1994; Wang & McGinty, 1996; Ishida et al., 1998). Second, damage to corticostriatal afferents, which are mostly glutamatergic, reduces IEG expression evoked by amphetamine (Cenci & Bjorklund, 1993; Cenci & Bjorklund, 1994). Third, activation of corticostriatal fibres by electrical stimulation induces c-fos mRNA or Fos-IR in the striatum and STN (Fu & Beckstead, 1992;...
Wan et al., 1992; Liste et al., 1995; Parthasarathy & Graybiel, 1997; Sgambato et al., 1997), and this effect is attenuated by glutamate antagonists (Liste et al., 1995; Berretta et al., 1997). Fourth, local cortical disinhibition by application of the GABA-A antagonist, picrotoxin (Arnauld et al., 1996; Berretta et al., 1997; Berretta et al., 1999) or local infusion of glutamate agonists into the striatum, induces Fos-IR in ENK+, but not ENK−, neurons (Berretta et al., 1997). Fifth, when amphetamine or cocaine are given in a novel environment there is a massive increase in c-fos mRNA expression throughout the neocortex, including the prefrontal cortex and the amygdala, which in part may reflect activation of glutamatergic corticostriatal systems. This cortical activation is probably due the action of a novel environment as a stressor (Cullinan et al., 1995), because mere exposure to a novel environment (without drug) increases corticosterone secretion and induces c-fos mRNA in the neocortex and portions of the amygdala (Badiani et al., 1998; Uslaner FIG. 2.

![Image]

**FIG. 2.**

![Image]

**FIG. 3.**

![Image]

**FIG. 4.**
We hypothesize therefore that when amphetamine and cocaine are given in a novel environment, the primary neuropharmacological effects of these drugs on monoamine neurotransmission (which predominate in the home condition) interact with the effects of environmental novelty on corticostriatal glutamate systems, and this interaction leads to the recruitment of the ENK+ cell population in the striatum. The identity of the neurotransmitter systems that engage corticostriatal cells is unknown, but neurotransmitter systems activated by stressors, such as monoamines, are prime suspects. Note, however, that the cortical activation produced by exposure to a novel environment alone (in the absence of drugs) is not sufficient to engage ENK+ cells or the STN (see Figs 1B and 3). This appears to require a drug–environment interaction at the level of the striatum, and we hypothesize this involves a monoamine–glutamate interaction.

Finally, it is tempting to speculate that engaging the ENK+ cell population in the striatum leads to increased activity in the ‘indirect’ pathway, and that this accounts for the increase in c-fos mRNA expression in the STN seen when amphetamine or cocaine are given in a novel environment. It has been reported previously that amphetamine increases Fos-IR (Wirtshafter & Asin, 1999), glucose utilization (Trugman & James, 1993; Pontieri et al., 1995) and unit activity (Olds et al., 1999) in the STN, although in these studies the effect of environmental context was not examined. Of course, it is also possible that the effect of environmental novelty on psychostimulant-evoked c-fos mRNA expression in the STN is not related directly to the recruitment of ENK+ cells in the striatum, but to activation of one or many other afferents to the STN, including those arising in the neocortex (for review seeParent & Hazrati, 1995).

It is worth noting that the monoamine–glutamate interaction hypothesized here may not only facilitate striatal and STN IEG expression, but because psychostimulant administration in a novel environment facilitates behavioural sensitization (Badiani et al., 1995a; Crombag et al., 1996; Brownman et al., 1998), it may also promote drug experience-dependent neuroplasticity. Indeed, stimulation of the STN can produce long-term potentiation (LTP)-like changes in the substantia nigra (Overton et al., 1999). This is important because of the proposed relationship between LTP, sensitization and glutamate neurotransmission (Wolf, 1998).

Conclusions

In conclusion, the pattern of gene expression induced by psychostimulant drugs is determined, to an amazing extent, by the setting in which these drugs are experienced. This may account for some of the effects of environmental novelty on both the acute psychomotor actions of these agents, as well as their ability to induce drug experience-dependent neuroplasticity. Most importantly, these data indicate that to understand the neurobiological actions of drugs of abuse that are critical in the development of addiction, such as their ability to promote neuroplasticity, we must pay close attention not only to their direct pharmacological actions, but also, as put by Falk & Feingold (1987, p. 1503), to the ‘cluster of interactions among the pharmacological substance, the individual set of the organism, and the environmental setting’.

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Abbreviations

- 6-OHDA, 6-hydroxydopamine; DA, dopamine; DYN, dynorphin; ENK, enkephalin; IEGs, immediate early genes; i.p., intraperitoneal; IR, immunoreactivity; LTP, long-term potentiation; neg, negative; pos, positive; STN, subthalamic nucleus.

References


Environmental context and gene expression 1983