Dopamine D4 receptor-mediated presynaptic inhibition of GABAergic transmission in the rat supraoptic nucleus

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Abstract

The mechanism by which dopamine induces or facilitates neurohypophysial hormone release is not completely understood. Because oxytocin- and vasopressin-secreting supraoptic neurons are under the control of a prominent GABAergic inhibition, we investigated the possibility that dopamine exerts its action by modulating GABA-mediated transmission. Whole-cell voltage-clamp recordings of supraoptic neurons were carried out in acute hypothalamic slices to determine the action of dopamine on inhibitory postsynaptic currents. Application of dopamine caused a consistent and reversible reduction in the frequency, but not the amplitude, of miniature synaptic events indicating that dopamine was acting presynaptically to reduce GABAergic transmission. The subtype of dopamine receptor involved in this response was characterized pharmacologically. Dopamine inhibitory action was greatly reduced by two highly selective D4 receptor antagonists L745,870, L750,667 and to a lower extent by the antipsychotic drug clozapine but was unaffected by SCH 23390 and sulpiride, D1/D5 and D2/D3 receptor antagonists respectively. In agreement with these results, the action of dopamine was mimicked by the potent D4 receptor agonist PD168077 but not by SKF81297 and bromocriptine, D1/D5 and D2/D3 receptor agonists respectively. Dopamine and PD168077 also reduced the amplitude of evoked-IPSCs, an effect that was accompanied by an increase in paired-pulse facilitation. These data clearly indicate that D4 receptors are located on GABA terminals in the supraoptic nucleus and that their activation reduces GABA release in the supraoptic nucleus. Therefore, dopaminergic facilitation of neurohypophysial hormone release appears to result, at least in part, from disinhibition of magnocellular neurons caused by the depression of GABAergic transmission.
Introduction

The supraoptic nucleus of the hypothalamus is part of the hypothalamo-neurohypophysial system. It consists of magnocellular neurons that synthesize and secrete either oxytocin (OT) or vasopressin (VP). These neurons project their axons into the neural lobe where the neurohypophysial hormones are released directly in the bloodstream. Whereas VP is essential to body fluid homeostasis, OT is involved in reproductive functions, such as lactation and parturition. Secretion of the two hormones is controlled by the electrical activity of magnocellular neurons (Poulain and Wakerley, 1982) which itself is dependent upon afferent excitatory and inhibitory synaptic inputs originating from many brain areas (Anderson et al, 1990). \( \gamma \)-amino butyric acid (GABA) and glutamate are the main inhibitory and excitatory transmitters in the hypothalamus respectively (Decavel and Van den Pol, 1990; Van den Pol et al, 1990). Electrophysiological recordings have indicated the presence of functional GABA-A receptors on SON neurons responsible for fast inhibitory potentials (Randle et al, 1986). GABA-B receptors have also been reported in the SON on both glutamatergic and GABAergic terminals (Kombian et al, 1996; Mouginot et al, 1998) and on magnocellular neurons (Harayama et al, 1998; Stern et al, 2002). Studies performed at the ultrastructural level have revealed that over 40% of all synapses on magnocellular neurons were GABAergic (Gies and Theodosis, 1994). Accordingly, GABA has been reported to play an important role in the regulation of firing activity both in OT and VP SON neurons (reviewed in Renaud and Bourque, 1991).

In addition to the transmitters GABA and glutamate, several other substances have been described as neuromodulators in the SON (Renaud and Bourque, 1991). One of them is dopamine (DA) that acts on a variety of G-protein coupled receptor
subtypes classified in 2 families. The D1 family includes D1 and D5 receptors whereas
the D2 family consists of D2, D3 and D4 receptors. The D1 and D2 families have been
reported to be positively and negatively coupled to adenylyl cyclase respectively
(Missale et al, 1998). The supraoptic nucleus receives a diffuse dopaminergic
innervation from cells located in the A14 and A15 regions (Van Vulpen et al, 1999;
Jourdain et al, 1999). Moreover, dopaminergic synapses have been documented on
dendrites and soma of SON neurons (Buijs et al, 1984; Decavel et al, 1987). In vivo
experiments have shown that intracerebroventricular (Bridges et al, 1976; Moos and
Richard, 1982) or direct injection of DA into the SON (Urano and Kobayashi, 1978)
could induce or facilitate the release of neurohypophysial hormones. In lactating rats,
OT release is facilitated or inhibited through the activation of D1 or D2 receptors
respectively (Crowley et al, 1987; Parker and Crowley, 1992). In vitro, dopamine has
been reported to depolarize SON neurons directly through the activation of D2-like
receptors (Yang et al, 1991) whereas activation of presynaptic D4 receptors has been
found recently to inhibit glutamatergic transmission (Price and Pittman, 2001).

Because most of the studies performed in vivo points to a general excitatory
action of DA on the hypothalamo-neurohypophysial system, we tested the hypothesis
that DA could modulate inhibitory GABAergic inputs in the SON, as it is the case in other
brain regions (Miazaki and Lacey, 1998; Seamans et al, 2001, Gonzales-Islas and
Hablitz, 2001). Whole-cell patch clamp recordings performed in acute hypothalamic
slices indicated that application of DA resulted in a consistent and reversible reduction of
GABAergic synaptic activity. This inhibitory action appeared to be mediated, at least in
part, by the activation of presynaptic D4 receptors in agreement with the presence of
these receptors in the SON (Defagot et al, 1997).
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Methods

Preparation of hypothalamic slices:

Acute hypothalamic slices were obtained using procedures similar to those described previously (Oliet and Poulain, 1999). Briefly, female Wistar rats (1-2 months old) were anaesthetized and decapitated. The brain was quickly removed and placed in ice-cold artificial cerebrospinal fluid (ACSF) saturated with 95% CO₂ and 5% O₂. Thin coronal slices (300 µm) were cut with a vibratome (Leica) from a block of tissue containing the hypothalamus. Slices including the SON were hemisected along the midline and allowed to recover for at least 1 h before recording. A slice was then transferred into a recording chamber where it was submerged and continuously perfused (1-2 ml/min) with ACSF at room temperature. The composition of the ACSF was (in mM): 123 NaCl, 2.5 KCl, 1 Na₂HPO₄, 26.2 NaHCO₃, 1.3 MgCl₂, 2.5 CaCl₂ and 10 glucose (pH 7.4; 295-300 mosmol.kg⁻¹). In experiments in which L745,870 was bath-applied, a different ACSF was made in order to facilitate solubility of the drug. The composition of this solution was (in mM): 150 NaCl, 2.5 KCl, 1.2 KH₂PO₄, 10 HEPES, 1.3 MgSO₄, 2.5 CaCl₂ and 10 glucose (pH 7.4; 295-300 mosmol.kg⁻¹).

Patch-clamp recording:

Magnocellular neurons were visually identified using infrared differential interference contrast microscopy (Olympus). Patch-clamp recording pipettes (3-5 MΩ) were filled with a solution containing (in mM): 141 CsCl, 10 HEPES, 5 QX 314 and 2 Mg-ATP (adjusted to pH 7.1 with CsOH). Membrane currents were recorded using an Axopatch-1D amplifier (Axon Instruments, Inc). Signals were filtered at 2kHz and digitised at 5kHz via a DigiData 1200 interface (Axon Instruments, Inc.). Series
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resistance (6-20 MΩ) was monitored online and cells were excluded from data analysis if more than a 15% change occurred during the course of the experiment. All cells were held at -60 mV in voltage clamp mode. Spontaneous unitary synaptic currents (miniatures) obtained in the presence of tetrodotoxin (TTX) were stored on videotape via a pulse-code modulator (Neurodata Corp.), detected and analysed off-line using Axograph (Axon Instruments, Inc.). To evoke synaptic responses, a glass stimulating electrode filled with ACSF and connected to an isolated stimulator (Digitimer Ltd) was placed in the hypothalamic region dorsomedial to the SON, as described previously (Kombian et al, 1996). Synaptic responses were evoked at 0.05 Hz, using square pulses of 0.1 ms duration, and analyzed online using pClamp (Axon Instruments, Inc). To study the paired-pulse facilitation ratio (PPF ratio), two synaptic responses (S1 and S2) were evoked by a couple of stimuli given at 60 ms intervals. PPF ratio was expressed as the ratio of the amplitude of the second synaptic response over the first synaptic response (S2/S1).

Data were compared statistically with either the paired or the unpaired Student’s t-test accordingly. Miniature amplitude and frequency distributions were compared using the non-parametric Kolmogorov-Smirnov test. Significance was assessed at P<0.05. All data are reported as mean ± S.E.M.

Drugs

All drugs were bath-applied. Appropriate stock solutions were made and diluted with ACSF just before application. QX-314 chloride (Alomone labs) was diluted directly in the patch-solution. Drugs used were 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, RBI), bicuculline methobromide, bromocriptine (Tocris), clozapine, dopamine, L750,667,
L745,870 (Sigma), PD168077, SCH 23390, SKF 38393 (Tocris), sulpiride and TTX (Sigma).
Results

Whole-cell voltage-clamp recordings were obtained from 74 supraoptic neurons in the presence of 10 mM CNQX and 0.5 mM TTX in the external solution, inwardly going spontaneous synaptic currents were recorded at a holding potential of –60 mV. These events were completely abolished by bath-application of bicuculline (20 μM; fig. 1A) and had a reversal potential close to 0 mV (not shown) in agreement with the equilibrium potential for chloride ions in our experimental conditions. Taken together these findings indicated that these unitary currents were entirely mediated by the activation of GABA-A receptors (Randle et al, 1986). The mean frequency of mIPSCs varied greatly between neurons from 0.5 to 7.7 Hz whereas the mean amplitude ranged from –66.0 to –348.6 pA.

Dopamine inhibits mIPSCs

Bath-application of dopamine (DA; 300 μM) caused an important and reversible reduction of mIPSC activity (fig. 1B). This effect was associated with a rightward shift of the event interval distribution (fig. 1D; P<0.05), reflecting a decrease in mIPSC frequency. Conversely, DA neither affected the amplitude distribution (P>0.05) nor the kinetics of the mIPSCs, as illustrated in figure 1C. On average, DA significantly inhibited the frequency of mIPSCs by 60.8 ± 5.8 % (n=9; P<0.05; fig.1E) whereas the mean amplitude of these unitary events was not significantly affected (-7.2 ± 4.0 %; P>0.05). This specific modulation of mIPSC frequency is usually considered to reflect a presynaptic modulation of transmission (Redman, 1990). Our results, therefore, indicate that dopamine acts presynaptically to inhibit GABA release in the SON. Because DA did
not change the amplitude distribution or the kinetics of the unitary synaptic GABAergic currents, we have focused the rest of our study on mIPSC frequency except when otherwise stated.

We next investigated the dose-dependent profile of this inhibition by using varying concentrations of DA (fig.2A). The frequency of mIPSCs was reduced, on average, by $4.1 \pm 4.8\%$ (n=5 cells), $2.9 \pm 4.3\%$ (n=5), $53.0 \pm 7.0\%$ (n=5); $69.0 \pm 8.2\%$ (n=3) and $60.8 \pm 5.8\%$ (n=9) for 0.3, 3, 30, 100 and 300 μM dopamine, respectively. As illustrated in figure 2B, fitting these data with a Boltzmann function revealed values for half-maximal inhibition (IC50) of $20.8 \pm 2.2$ μM and a threshold of 3 μM. Maximal inhibitory responses were obtained for concentrations of 100 μM or above.

Dopamine-mediated inhibition of mIPSCs is affected by D4 receptor antagonist

In order to identify the subtype of receptor involved in the modulation of inhibitory GABAergic transmission by DA, we used several dopaminergic antagonists. In this set of experiments, the antagonist was first added to the bathing solution and DA (300 μM) was subsequently applied (fig.3A and 3B). In the presence of the D2/D3 receptor antagonist sulpiride (10 μM), dopamine retained its full ability to inhibit mIPSC frequency (-57.6 ± 0.7 %; n=4; P>0.05). Similarly, blockade of D1/D5 receptors with SCH 23390 (100 μM) failed to prevent the dopamine-dependent inhibition (-62.0 ± 0.7 %; n=4; P>0.05). These findings suggested that D1, D2, D3, and D5 receptors are not implicated in the inhibitory response induced by DA. We next investigated whether D4 dopamine receptors could be involved in the inhibition of GABA release since it has been recently reported that activation of these receptors inhibited glutamate release in the SON (Price
and Pittman, 2001). Interestingly, in the presence of the atypical antipsychotic drug clozapine (50 μM), an antagonist of dopamine receptors that has a higher affinity than for D4 over D2/D3 receptors (Seeman and Van Tol, 1994), dopamine-induced inhibition of mIPSC frequency was partially prevented (-39.9 ± 4.3 %; n=6; P<0.05). The involvement of D4 receptors was confirmed by the use of L750,667 and L745,870, two highly specific antagonists of these receptors (Kulagowski et al, 1996; Patel et al, 1996). In the presence of L750,667 (50 μM) and L745,870 (50 μM), dopamine reduced mIPSC frequency by 27.7 ± 6.4 % (n=6) and 19.8 ± 5.6 % (n=5) respectively (fig. 3A and 3B). These values were significantly different from those obtained by DA alone in the absence of these antagonists (P<0.05) indicating that D4 receptors mediate part of, if not all, the action of dopamine on mIPSCs in the SON. Neither clozapine, L750,667 nor L745,870 affected mIPSC frequency by themselves, suggesting that D4 receptors were not activated tonically by endogenous dopamine.

*Dopamine-mediated inhibition of mIPSCs is mimicked by a D4 receptor agonist*

If D4 receptors mediate the inhibition of GABAergic transmission, a specific agonist of this receptor subtype should mimic this action. On the other hand, agonists of D1, D2, D3, and D5 receptors should be without effect on GABAergic synaptic currents. We first examined the action of PD168077, a potent and selective D4 receptor agonist (Glase et al, 1997). Bath-application of PD168077 (30 μM; n=8) reduced the frequency (-51.6 ± 4.2 %; P<0.05) but not the amplitude (-3.6 ± 1.8 %; P>0.05) of mIPSCs (fig.4). This finding confirms the existence of presynaptic D4 receptors on GABAergic terminals in the SON whose activation leads to an inhibition of transmitter release. Conversely,
exposure of SON neurons to SKF 38393 (30 μM; n=4), a specific D1/D5 receptor agonist, and bromocriptine (50 μM; n=4), a specific D2/D3 receptor agonist, was without effect on mIPSC frequency (-5.2 ± 6.7 % and -2.1± 4.4 % respectively; P>0.05; fig. 4D). Taken together, these data indicate that, in the SON, indeed dopamine inhibits mIPSCs through the activation of D4 receptors.

*Dopamine-mediated inhibition of evoked-IPSC amplitude*

Although our data indicate that DA inhibits spontaneous GABA-A receptor-mediated currents, it remained to be determined whether GABA release evoked by electrical stimulation was also sensitive to dopamine. As illustrated in figure 5A and 5B, bath-application of DA (300 μM) was found to reversibly reduce the amplitude of evoked-IPSCs by 60.5 ± 5.4 % (n=9). This inhibitory action of DA was accompanied by an increase in paired-pulse facilitation ratio from 1.21 ± 0.15 to 2.22 ± 0.34 (n=9; fig. 5C and 5D) as expected from a presynaptic reduction of transmitter release (Zucker and Regehr, 2002). To make sure that the action of DA on evoked-GABA release was mediated through D4 receptors, we tested the effect of PD168077 (30 μM) on evoked-IPSCs (fig. 5A and 5B). In the presence of the D4 agonist, the amplitude of the response was inhibited by 54.6 ± 8.6 % (n=5), an effect similar to that obtained with 300 μM DA. These results are in agreement with those obtained on mIPSCs and confirm the presence of presynaptic D4 receptors whose activation depresses the release of GABA in the SON.
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Discussion

Dopamine modulates GABA release in various brain regions such as the cortex (Seamans et al, 2001; Gonzales-Islas and Hablitz, 2001) and the substantia nigra (Miyazaki and Lacey, 1998). This disinhibitory process represents a potent regulatory mechanism of neuronal excitability. Our data indicate that, in the SON, it is through a similar mechanism that dopamine could contribute to the regulation of neurohypophysial hormone secretion (Bridges et al, 1976; Urano and Kobayashi, 1978; Moos and Richard, 1982; Forsling and Williams, 1984; Ivanyi et al, 1986; Yamagushi and Hama, 1989).

Presynaptic inhibition of GABAergic transmission

Suprathreshold applications of dopamine inhibited GABAergic synaptic currents in all SON neurons tested. Since we did not record from a specific area in the SON, it is very likely that DA modulates GABAergic transmission in both OT and VP neurons in agreement with the observation that DA modulates the release of both neurohypophysial hormones (Bridges et al, 1976; Moos and Richard, 1982).

The inhibitory action of DA was associated with a reduction in the frequency, but not the amplitude, of mIPSCs and with an increased paired-pulse facilitation of evoked-IPSCs. These findings are consistent with an inhibition of presynaptic origin (Redman, 1990; Zucker and Regehr, 2002). DA receptors mediating this action are almost certainly located on the terminals rather than on the cell bodies of GABAergic neurons since mIPSCs were obtained in the absence of presynaptic action potentials due to the blockade of voltage-gated Na⁺ channels by TTX. The mechanism by which activation of presynaptic DA receptors elicits an inhibition of GABA release remains to be determined. One possible explanation could be an inhibition of the voltage-gated Ca²⁺
channels involved in transmitter release (Mei et al, 1995). The reduction of Ca\(^{2+}\) entry in
the terminals would alter the coupling between action potential and exocytosis of
vesicles (Augustine et al, 1987). However, this mechanism cannot account for the
reduction of mIPSC activity in the present study since these unitary events are known to
be independent of Ca\(^{2+}\)-entry (Brussaard et al, 1996; Oliet and Poulain, 1999).

Alternatively, the activation of presynaptic DA receptors could affect the proteins
involved in the intracellular signaling cascade leading to exocytosis. Since most of the
effects of dopamine are associated with the modulation of a cAMP-dependent protein
kinase (PKA; Missale et al, 1998), and since transmitter release has been shown to be
sensitive to PKA (Trudeau et al, 1996; Kondo et al, 1997), the action of DA observed in
our experiments could reflect a change in cAMP level in the terminals. Interestingly,
the presynaptic inhibition of GABAergic release in the SON appears to be inhibited through
the activation of several presynaptic receptors coupled to adenylyl cyclase activity. This
includes group III mGlurS (Schrader and Tasker, 1997; Piet et al, 2003), GABA-B
(Mouginot et al, 1998) and adenosine A1 (Oliet and Poulain, 1999) receptors. It is also
possible that other intracellular signaling mediators, like protein kinase C, are involved in
this process.

**Receptor identification**

To identify the dopamine receptors involved in the inhibition of GABA release, we
used various antagonists and agonists exhibiting different selectivity for DA receptor
subtypes. In all likelihood, the receptor responsible for inhibition of mIPSC activity is the
D4 receptor. This is based on the sensitivity of DA-induced response to L750,667 and
L745,870, which are specific D4 antagonists, and on the observation that the specific D4
agonist PD168077 mimicked DA inhibitory action on both miniatures and evoked-IPSCs. This finding was strengthened by the lack of effect of sulpiride and SCH 23390, D2/D3 and D1/D5 antagonists respectively, on DA-mediated inhibition of GABAergic transmission. Furthermore, SKF 81297 and bromocriptine, D1/D5 and D2/D3 specific agonists respectively, did not affect mIPSC activity. Finally, clozapine, an antagonist that has a 10-fold greater affinity for D4 than D2 and D3 receptors (Seeman and Van Tol, 1994), was able to partially prevent the inhibitory action of DA. Taken together, these results demonstrate that DA-induced inhibition of GABA release in the SON is mediated by the activation of dopamine D4 receptors. Dopamine D4 receptor activation has also been reported to inhibit GABAergic transmission in the prefrontal cortex through a PKA-dependent mechanism (Wang et al, 2002) but in this structure, D4 receptor appears to have an action on postsynaptic GABA-A receptors rather than on transmitter release.

**Functional implications**

The inhibitory action of DA on GABAergic transmission in the SON neurons should lead to a disinhibition of magnocellular neurons, and, as a consequence, to an augmented excitability of the hypothalamo-neurohypophysial system. This is in agreement with the excitatory effects observed *in vivo* in response to injections of DA in the SON or intracerebroventricularly (Bridges et al, 1976; Moos and Richard, 1982; Urano and Kobayashi, 1978). However, to understand better the action of DA in the SON, it is important to take into consideration the various actions of DA that have been reported in previous *in vitro* studies. In particular, it has been shown that DA, at concentrations similar to those used in the present study, inhibits glutamate release via the activation of presynaptic D4 receptors (Price and Pittman, 2001), an effect that
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should reduce cell excitability and hormone secretion. Conversely, DA within the same range of concentrations acts on postsynaptic D2 receptors causing a membrane depolarization due to the activation of a cationic conductance (Yang et al, 1991). In view of these different effects, the overall action of DA on SON neurons and its consequence on hypothalamo-neurohypophysial hormones secretion remains speculative. In particular, whether one of these dopamine responses is predominant in situ has to be determined. Inhibiting glutamatergic and GABAergic synaptic activity, and therefore reducing background synaptic noise, could have several consequences on the postsynaptic cell. It could make the neuron more electrically compact by increasing input resistance (Paré et al, 1997), reduce shunting inhibition and increase the gain of the input-output neuronal response (Chance et al, 2002; Prescott and De Koninck, 2003) as well as render the cell less sensitive to weak signals (Wiesenfeld and Moss, 1995). One attractive hypothesis could be that DA-mediated inhibition of both GABA and glutamate synaptic activities in the SON isolates, to some extent, the neurons from excitatory and inhibitory drives mediated through these inputs. This will make SON neurons more responsive to the activation of D2 postsynaptic receptors, for instance. In other words, this process could serve to significantly enhance the signal-to-noise ratio for the information originating from dopaminergic inputs.

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Figure legends

Figure 1: Dopamine reversibly inhibits mIPSCs. A: Example of a recording where bicuculline (20 μM) was bath-applied resulting in a complete inhibition of synaptic activity. B: Consecutive traces showing typical mIPSC activity recorded before, during and after application of 300 μM DA. Cumulative plots of amplitude (C) and event interval (D) distributions before (thick line) and during (thin line) DA application for the cell illustrated in B. Whereas DA did not affect mIPSC amplitude, it caused the event interval distribution to be shifted towards the right, reflecting a reduced mIPSC frequency. The inset in C shows a superimposition of averaged traces of mIPSCs obtained in the presence and absence of DA for the cell illustrated in B. Summary histogram obtained from 9 different neurons is shown in E, illustrating the percent change in mean amplitude (q) and frequency (Hz) of mIPSCs induced by DA.

Figure 2: DA-mediated effect on mIPSCs is dose-dependent. A: example of a recording where increasing concentrations of DA from 3 to 300 μM were consecutively applied. B: Data points are means of the percentage inhibition of IPSC frequency induced by the indicated DA concentration. These points were fitted with a Boltzmann function (line).
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Figure 3: Characterization of the dopamine receptor subtype responsible for the inhibition of mIPSCs. A: Example of recordings obtained from 5 different SON neurons where the action of DA (300 μM) was tested in the presence of SCH 23390 (100 μM), sulpiride (10 μM), clozapine (50 μM), L745,870 (50 μM) and L750,667 (50 μM). B: Summary histogram of DA-mediated inhibition of mIPSC frequency in the presence of various dopaminergic receptor antagonists. DA-mediated inhibition was significantly affected by clozapine, L750,667 and L745,870 but not by SCH 23390 or sulpiride. Number of cells are indicated above the bars.

Figure 4: Effect of a D4-dopaminergic receptor agonist on mIPSC activity. A: Consecutive traces showing typical mIPSCs before and during application of 30 μM PD168077. B: cumulative plots of amplitude distribution was similar before (thick line) and during (thin line) PD168077 application for cell illustrated in A. C: PD168077 caused the event interval distribution to be shifted towards the right, indicating a decrease in mIPSC frequency. D: Summary histogram of the effect of various DA receptor agonists on mIPSC frequency. Application of SKF 38393 (30 μM) and bromocriptine (50 μM) did not affect mIPSC activity whereas PD168077 (30 μM) significantly reduced the frequency of these events like DA. Number of cells are indicated above the bars.

Figure 5: Effect of dopamine on evoked-IPSC. A: examples of recordings where applications of 300 μM DA (upper panel) and 30 μM PD168077 (lower panel) reversibly reduced the amplitude of evoked-IPSC. B: Summary histogram illustrating the inhibitory action of DA and PD 168077 on evoked-IPSC amplitude. C: Example of a recording
where pairs of stimulation were applied at 60 ms interval in the presence and absence of DA (upper panel). Superimposition of the two traces scaled to the first IPSC obtained in absence of DA reveals that PPF ratio is increased (lower panel). D: Summary histogram illustrating the increased in PPF ratio induced by DA.
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Figure 1 (Azdad et al)
Inhibition of IPSC by dopamine in the supraoptic nucleus

A

control

DA 3 μM

DA 30 μM

DA 300 μM

200 pA

1 s

B

inhibition of mIPSC frequency (%)

80

60

40

20

0

0.1 1 10 100 1000

dopamine in [μM]

figure 2 (Azdad et al)
Inhibition of IPSC by dopamine in the supraoptic nucleus

Figure 3 (Azdad et al)
Inhibition of IPSC by dopamine in the supraoptic nucleus

A

control

PD168077

B

control

PD168077

C

control

PD168077

D

n=8

* 

n=4

n=4

inhibition of mIPSC frequency (%) 

PD168077

SKF 38393

bromocriptine

figure 4 (Azdad et al)
Inhibition of IPSC by dopamine in the supraoptic nucleus

A

control DA wash

control PD168077 wash

100 pA

20 ms

B

n=9

n=5

inhibition of evoked-IPSC amplitude (%)

DA PD168077

C

control DA

100 pA

20 ms

scaled

D

PPF ratio

control DA

* figure 5 (Azdad et al)