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# Effects of physiological and pharmacological stimuli on dopamine release in the rat globus pallidus

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**Abstract**

A major aspect of understanding functions of the globus pallidus (GP) within the basal ganglia is the significance of its dopamine innervation. Here, we used in vivo-microdialysis in rats to characterize pallidal dopamine release in response to a number of physiological and pharmacological stimuli known to activate dopamine neurons. Results reveal that an aversive stimulus, i.e. handling for 20 min, significantly increased dialysate dopamine in the globus pallidus to about 130% of baseline levels. Likewise, a novel and appetitive stimulus, i.e. presentation of unfamiliar, palatable food, significantly elevated pallidal dopamine to about 150% of baseline levels both in rats which did and did not consume the food reward. These findings provide evidence that increases of dopamine (DA) efflux may largely reflect stimulus saliency implicating an involvement of pallidal dopamine signalling in control of behaviour governed by salient stimuli. Results further showed that reverse microdialysis of D-amphetamine and cocaine in augmenting concentrations of 0.1–100 μM elevated dialysate dopamine in a concentration-dependent manner suggesting a role of pallidal dopamine in mediating behavioural effects of psychostimulant drugs.


*Keywords:* Globus pallidus; Microdialysis; Handling; Food; D-Amphetamine; Cocaine

## 1. Introduction

The globus pallidus (GP), the rodent homologue of the primate external part of the globus pallidus (GPe), is an integral component of the indirect pathway of the basal ganglia connecting the caudate-putamen (CPu) with the substantia nigra pars reticulata and the nucleus entopeduncularis (Parent and Hazrati, 1995). Increasing evidence suggests that the GP is not solely a relay station but rather in a strategic position to control basal ganglia information flow (Chesselet and Delfs, 1996).

An important and largely neglected aspect of understanding pallidal functions within the basal ganglia is the significance of its dopamine (DA) innervation which arises from substantia nigra pars compacta neurons (Fallon and Moore, 1978; Lindvall and Bjorklund, 1979; Cossette et al., 1999). The GP displays tyrosine hydroxylase immunoreactive fibres and varicosities (Arluison et al., 1984; Gaykema and Zaborszky, 1996) and expresses DA D1, D2, D3, D4 and D5 receptors (Martres et al., 1985; Richfield et al., 1987; Mansour et al., 1990; Bouthenet et al., 1991; Larson and Ariano, 1995; Mrzljak et al., 1996; Gurevich and Joyce, 1999; Ciliax et al., 2000). In addition, DA reuptake transporters (Mennicken et al., 1992) and monoaminoxidase activity (Saura et al., 1992) have been detected in the GP. Neurochemical, electrophysiological and behavioural data provide evidence that the DA innervation of the GP is functional. Using in vivo-microdialysis, we demonstrated that pallidal DA is of neuronal origin, released impulse-dependently and responsive to rewarding stimuli (Hauber and Fuchs, 2000; Fuchs and Hauber, 2004). Moreover, intra-GP infusion of DA drugs altered firing rate and pattern of pallidal neurons (Bergstrom and Walters, 1984; Napier et al., 1991) as well as behaviour in rats (Ernst and Smelik, 1968;

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Costall et al., 1972; Koshikawa et al., 1990a,b; Hauber and Lutz, 1999a,b; Galvan et al., 2001).

For a further understanding of the significance of pallidal DA signalling, the present study sought to characterize effects of physiological and pharmacological stimuli on DA transmission in the GP. In the first experiment, we investigated how pallidal DA release is influenced by presentation of an appetitive, novel stimulus (palatable, unfamiliar food) and an aversive stimulus (prolonged handling), i.e. stimuli known to increase DA efflux in the nucleus accumbens (ACB) or prefrontal cortex (PFC) (Bassareo and Di Chiara, 1997; Feenstra et al., 1998). In the second experiment, we investigated how pallidal DA release is altered by reverse microdialysis of cocaine and D-amphetamine, i.e. psychostimulant drugs which markedly enhance DA efflux (Pierce and Kalivas, 1997; Hedou et al., 1999).

## 2. Materials and methods

### 2.1. Subjects

Male CD rats (Charles River, Sulzfeld, Germany) were used for all experiments and housed in groups of five animals in transparent macrolon cages (type IV; 35 cm × 55 cm × 10 cm; Ebeco, Castrop-Rauxel, Germany) in a 12-h light:12-h dark cycle before surgery. Temperature (20 ± 2 °C) and humidity (50 ± 10%) were kept constant in the animal house. Rats were given ad libitum access to water and food (standard maintenance chow, Altromin, Lage, Germany). Experiments were conducted in accordance with the German Law on Animal Protection and approved by the proper authorities in Stuttgart, Germany.

### 2.2. Stereotaxic surgery

For stereotaxic surgery, animals were anaesthetized with sodium pentobarbital (60 mg/kg, i.p.) (Sigma–Aldrich, Taufkirchen, Germany) following pretreatment with atropine sulphate (0.5 mg/kg, i.p.) (Sigma–Aldrich) and secured in a Kopf stereotaxic apparatus (Kopf Instruments, Tujunga, USA). Animals ($N = 10$) weighing 220–270 g were implanted unilaterally with intracranial guide cannulae (CMA/12, CMA, Solna, Sweden) aiming to the GP at the following coordinates (Paxinos and Watson, 1986): AP −1.1 mm, L 2.5 mm and V −4.5 mm (from dura). After surgery rats were housed individually in macrolon cages (type III; 37 cm × 21 cm × 30 cm; Ebeco, Castrop-Rauxel) with raised solid-walled lids. Each rat was given at least 1 week to recover from surgery.

### 2.3. Microdialysis

Microdialysis was performed in the home cage of an animal with the lid replaced by a metal frame bearing a counter-balanced arm with the swivel assembly. Dual channel low torque liquid swivels (75/D22/QM, Instech Labs., Plymouth Meeting, USA) were used. Attachment to the swivel was achieved by a spring tether connected directly to the head mount via a self-made plug. A microdialysis probe (CMA/12, CMA, Solna, Sweden; exposed membrane length 2 mm) was inserted through the guide cannula 12–14 h before the first baseline sample and perfused with artificial cerebrospinal fluid (aCSF) (147 mM $Na^+$, 3 mM $K^+$, 1.2 mM $Ca^{2+}$ and 1 mM $Mg^{2+}$) overnight using a CMA/100 microdialysis pump (CMA, Solna, Sweden) at 2.0 μl/min. Samples were collected every 20 min.

### 2.4. Drugs

Stock solutions of D-amphetamine sulfate (Sigma–Aldrich) and cocaine hydrochloride (Merck, Darmstadt, Germany) at concentrations of 10 mM were prepared in aCSF and stored in frozen (−70 °C) aliquots.

### 2.5. Microdialysis experiments with physiological stimuli

At the beginning of the experiments food pellets were removed from the home cage, water was permanently available. Subsequently, sampling of dialysates from the GP was started; samples were collected every 20 min. Five samples were taken until rats ($N = 10$) were exposed to a physiological stimulus. Two different physiological stimuli were tested, each animal was exposed to one stimulus only: (I) Handling, i.e. a rat ($N = 5$) was picked up, handled gently for 20 min (i.e. for one sample) within a towel and put back in the home cage (Feenstra and Botterblom, 1996). If mild restriction did not prevent the rat from jumping back into the home cage, it was picked up from there immediately. (II) Unfamiliar, palatable food consisting of three to four pieces (approx. 3 g) of Fonzies® (snack food, kindly provided by UB Snack Food, Donauwoerth, Germany)(Bassareo and Di Chiara, 1999). Fonzies were given to the rat ($N = 5$) for 20 min in the home cage and removed afterwards. The amount of Fonzies eaten was estimated by calculating the food weight difference.

### 2.6. Microdialysis experiments with pharmacological stimuli

A subset of animals with pallidal probes ($N = 6$) exposed to physiological stimuli were subsequently tested for the effects of pharmacological stimuli. Three hours after handling or Fonzies feeding, they received either D-amphetamine ($N = 3$) or cocaine ($N = 3$) via reverse microdialysis into the GP in a cumulative manner. Increasing concentrations (0.1, 1, 10 and 100 μM) of each compound were added to the perfusion fluid for 60 min each, followed by 1 h with perfusion fluid alone.

### 2.7. Analytical procedure

Dialysates were analysed for DA, DOPAC and HVA using HPLC with electrochemical detection. The mobile phase consisted of 2 g/l sodium acetate, 5 g/l citric acid, 2 g/l 1-heptanesulfonic acid, 110 mg/l $Na_2$-EDTA and 18.5% (v/v) methanol with pH at 3.9 before methanol was added. Minor modifications in the concentrations of HSA and methanol were made to optimise DA peak separation if necessary. The HPLC apparatus consisted of a Flux Rheos 2000 pump (Flux Instruments, Basel, Switzerland), a refrigerated CMA/200 autosampler (CMA, Solna, Sweden), a Nucleosil $C_{18}$ column (Bischoff, Leonberg, Germany; 5 μm particles, length × i.d. 125 mm × 3 mm) and a dual electrode BAS LC4C amperometric detector (Bioanalytical Systems, Lafayette, USA) with the electrode potential set to 600 mV at high gain to quantify DA and 700 mV at a lower gain to measure the metabolites. Filter setting was 0.1 Hz and the separation was performed at room temperature. The detection limit of DA in a solution with standards was routinely about 2 pg per injection or lower.

### 2.8. Reconstruction of probe location

After the experiments, animals were killed by an overdose of pentobarbital, brains were removed, fixed for at least 2 h in formalin and immersed in 30% (w/v) sucrose for several days. Cryosections (60 μm) were taken and stained with cresyl violet. The location of microdialysis probes from all animals is shown in Fig. 1.

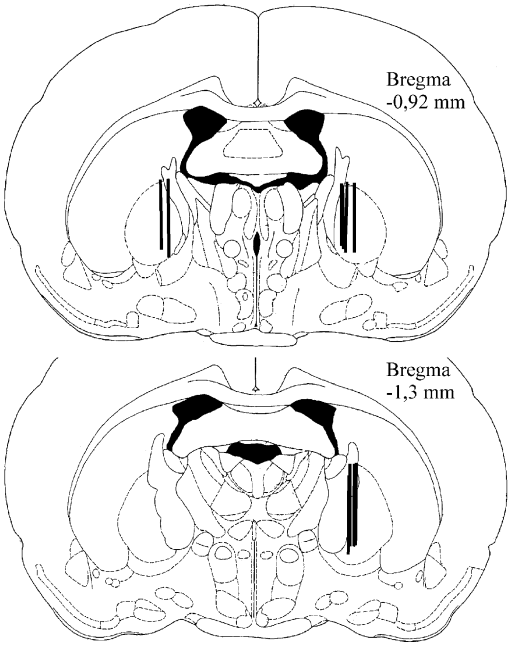


Fig. 1. Location of microdialysis probes in the GP reconstructed on the basis of coronal sections according to the atlas of Paxinos and Watson (1986); only the dialyzing part of the probe is shown in a representative plane.

### 2.9. Data expression and statistics

Data are expressed as percentages of control values (± standard error of the mean, S.E.M.). The mean DA dialysate concentrations of the three samples before presentation of physiological stimuli or pharmacological stimuli was taken as control and set to 100%. Data from serial DA assays after presentation of physiological stimuli (Fonzies, handling) were subjected to separate ANOVAs for repeated measures over time. Significant main effects were further analysed by a Dunnett's post hoc-test with the last baseline sample as reference. Likewise, data from serial DA assays after presentation of pharmacological stimuli (amphetamine, cocaine) were subjected to an ANOVA for repeated measures over time. Significant main effects and interactions were further analysed by a Tukey HSD post hoc-test. All statistical computations were carried out with STATISTICA™ (Version 6.1, StatSoft®, Inc., Tulsa, USA). The level of statistical significance (α-level) was set at $p < 0.05$.

## 3. Results

### 3.1. Effects of Fonzies feeding and handling on pallidal DA

The mean dialysate DA concentration (±S.E.M.) of all baseline samples from the GP prior to stimulus presentation was 3.24 ± 0.13 pg/20 μl ($N = 10$). Presentation of Fonzies elicited sniffing behaviour in all animals, three out of five animals started to ingest Fonzies within 5 min. The total amount of Fonzies consumed within 20 min was 1.6 ± 0.4 g (mean ± S.E.M., $N = 3$). Two animals did not ingest Fonzies, but exhibited behavioural activation during their presentation. After removal of Fonzies, all animals displayed increased locomotion, sniffing and drinking behaviour for about 30–60 min. Dialysate DA was significantly elevated in all animals after presentation of Fonzies to about 130% of basal values ($F_{(1,10)} = 4.41$, $p = 0.00034$, ANOVA, $N = 5$) (Fig. 2A). DA dialysate levels in animals which did and did not ingest Fonzies showed no significant differences as revealed by a Kruskal–Wallis ANOVA ($\chi = 2.22$, $p = 0.13$). During handling rats showed arousal, periods of behavioral activity and inactivity, but rarely tried to escape from handling. Handling for 20 min resulted in a significant increase in pallidal DA ($F_{(10,20)} = 8.23$, $p < 0.00004$, ANOVA, $N = 5$) to about 150% of the basal values as shown in Fig. 2B.

### 3.2. Effects of D-amphetamine and cocaine on pallidal GP

Perfusion of D-amphetamine ($N = 3$) and cocaine ($N = 3$) into the GP produced concentration-dependent increases in dialysate DA. ANOVA revealed significant main effects of drug ($F_{(1,4)} = 78.02$, $p < 0.0009$) and time ($F_{(17,68)} = 42.35$,

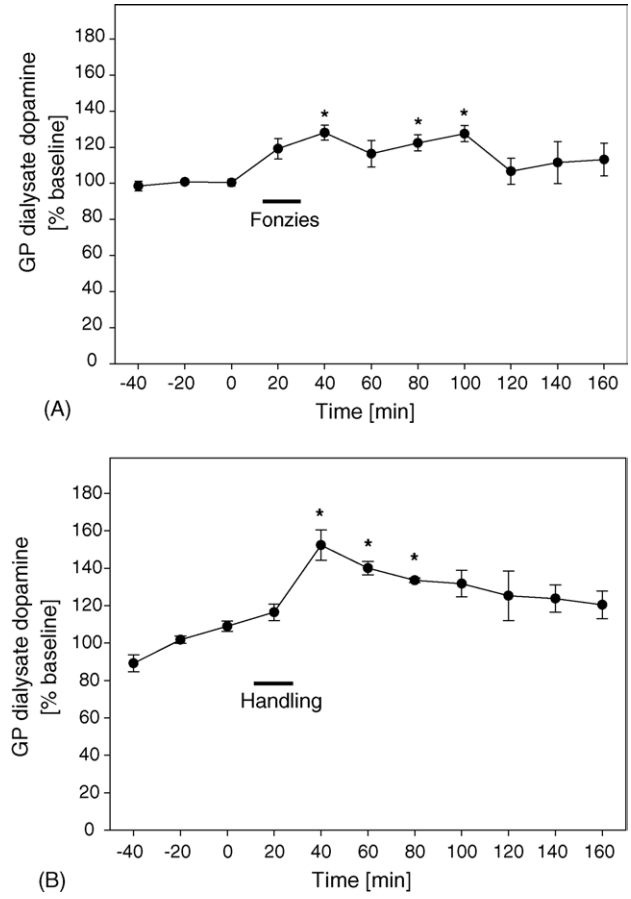


Fig. 2. Effects of feeding Fonzies (A) and handling (B) on dialysate DA levels in the GP. (*) Indicate significant differences ($p < 0.05$) compared to the basal value ($T = 0$ min). ANOVA followed by Dunnett's post hoc-test.

$p < 0.0001$) as well as a significant drug × time interaction ($F_{(17,68)} = 12.1$, $p < 0.0001$) (Fig. 3).

## 4. Discussion

Our present results demonstrate that presentation of an appetitive (novel, palatable food) or aversive stimulus (prolonged handling) as well as reverse microdialysis of D-amphetamine and cocaine elevated pallidal DA efflux. Thus, DA transmission in the GP appears to be responsive to a number of prototypical physiological and pharmacological stimuli known to elicit a DA release in the PFC, ACB or CPu.

### 4.1. Microdialysis in the GP

The GP is located in relative proximity to the CPu and bed nucleus of the stria terminalis (BNST) which both receive DA input. Therefore, DA diffusion from these areas could contribute to stimulus-induced changes of DA efflux measured here. However, this possibility is unlikely for several reasons. First, the time course of DA release gives no indication for diffusion. For instance, the increase in pallidal DA release after food presentation was not delayed, but started in the first sample period and the magnitude was comparable to other regions (Feenstra et al., 1998, 1999) and not lower as one would expect in case of diffusion from adjacent areas. Furthermore, diffusion coefficients of DA in brain tissue indicate that the amount of DA recovered by the dialysis membrane at a distance of 0.7 mm and more is

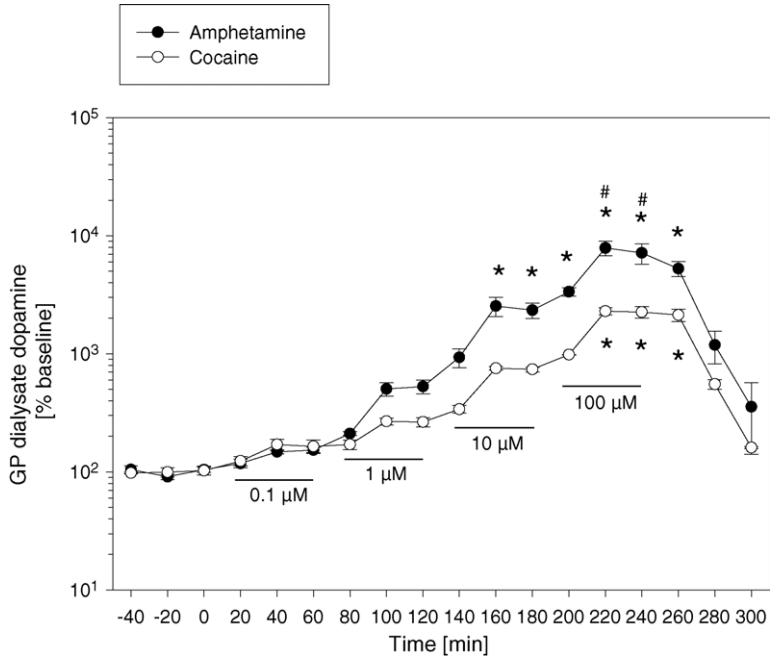


Fig. 3. Effect of perfusing D-amphetamine and cocaine on dialysate DA levels in the GP. (*) Indicates significant differences ($p < 0.05$) compared to respective basal value ($T = 0$ min), (#) indicates significant differences ($p < 0.05$) from corresponding time points of the amphetamine and cocaine group. ANOVA followed by a Tukey HSD post hoc-test.

minimal (Rice et al., 1985; Nicholson and Rice, 1986). In line with this notion, effects of cocaine or amphetamine on DA release in the adjacent core and shell subregion of the ACB were different (Pontieri et al., 1995). Hence, diffusion from the CPu and BNST which are about 1mm apart from dialysis probes in our experiment should be negligible, in particular as in areas with a dense DA innervation such as the CPu, effective reuptake mechanisms further limit diffusion. Moreover, drugs like amphetamine have rather slow penetration rates and relatively high perfusion concentrations are needed (1–10 mM) to reach substantial brain concentrations at a distance of 1 mm from the microdialysis probe (Westerink and De Vries, 2001). Taken together, we assume that changes of DA release recorded here are probably not the result of DA diffusion from adjacent areas receiving DA input.

### 4.2. Effects of physiological stimuli

Presentation of food reward can stimulate DA neurons and elevate DA release in the ACB, PFC or CPu (e.g. Joseph et al., 2003). Here, we observed that presentation of novel, palatable food (Fonzies) is also capable of increasing DA levels in the GP. Surprisingly, this occurred both in rats which did and did not ingest food. Therefore, rewarding qualities of food seem not to account for pallidal DA increase. On the other hand, we cannot rule out completely that the odour of Fonzies, even though unfamiliar to our rats, could be rewarding. Furthermore, we cannot exclude that rewarding food qualities could contribute to DA release in rats ingesting Fonzies as feeding with familiar food stimulated pallidal DA release in food-deprived rats (Hauber and Fuchs, 2000). However, this possibility seems unlikely as in the present study rats had ad libitum access to food, a condition in which substantial increases in DA release do not occur with food reward (for review, see Joseph et al., 2003).

Alternatively, the observed pallidal DA release in rats which did and did not ingest food could be related to the fact that salient events such as novel stimuli are also able to elicit a DA release (Feenstra et al., 1995; Feenstra and Botterblom, 1996; Bassareo and Di Chiara, 1999). Because of its unknown sensory properties and unexpected delivery, presentation of novel food was likely to be salient in our experiment. Thus, stimulus saliency and stimulus-induced exploratory behaviour might be major factors underlying the pallidal DA release seen here. However, this conclusion is preliminary and further experiments are required to elucidate in detail to which stimulus properties and behaviours pallidal DA release coincides as already done for feeding-induced DA release in other regions.

Another main findings of the current study is that an aversive stimulus, i.e. handling for 20 min (Feenstra et al., 1998), enhanced pallidal DA release. Previous studies indicated that a large category of aversive events appears capable of stimulating DA neurons and increasing DA release. For instance, handling (Feenstra et al., 1998; Feenstra et al., 1999) or restraint stress (Imperato et al., 1991) increased DA efflux in the ACB, intermittent tail-shock stress enhanced DA release in the CPu (Keefe et al., 1993) and foot shock or tail pinch activated mesolimbocortical and nigrostriatal DA neurons (Louilot et al., 1986; Young et al., 1993). The current observations extend these findings and show that an aversive event such as handling can stimulate DA release in the GP.

As salient and arousing events regardless whether they are appetitive or aversive stimulate DA activity (Horvitz, 2000), pallidal DA increases seen here could primarily reflect stimulus saliency. If so, DA signalling not only in the PFC, ACB or CPu (Horvitz, 2000), but also in the GP might play a role in control of behaviour governed by salient stimuli. There is consistent evidence that the GP (Costall and Olley, 1971; Cromwell and Berridge, 1997; Hauber et al., 1998) and its DA innervation (Ernst and Smelik, 1968; Costall et al., 1972; Koshikawa et al., 1990a,b; Hauber and Lutz, 1999a,b) regulates spontaneous motor behaviour in rats. In addition, lesion studies indicate that the GP subserves complex behaviour involving motivation and cognition (Morgane, 1961; Wyrwicka and Doty, 1966; Thompson et al., 1986; Everitt et al., 1987). However, it not known yet whether a blockade of pallidal DA transmission interferes with behavioural responses to environmental changes as suggested by our data.

### 4.3. Effects of pharmacological stimuli

Previous reports revealed that psychostimulant drugs enhanced extracellular DA levels in the ACB (Imperato et al., 1991; Bassareo and Di Chiara, 1997; Feenstra et al., 1998; Feenstra et al., 1999) or CPu (Hurd et al., 1988; Heidbreder et al., 1998; Mazei et al., 2002). The present study provides evidence that perfusion of D-amphetamine and cocaine produced a massive and concentration-dependent DA release in the GP as well. The fact that D-amphetamine had a greater potency than cocaine to increase pallidal DA efflux might be due to D-amphetamine's dual mode of action, i.e. reuptake inhibition and reverse operation of the DA transporter (DAT) (Zetterström et al., 1988; Arbuthnott et al., 1990; Bannon et al., 1995; Vizi et al., 2004), while cocaine acts primarily via inhibition of reuptake of DA released by neuronal stimulation (Bannon et al., 1995; Vizi et al., 2004). Our findings suggest that, to some extent, behavioural effects of psychostimulant drugs could be mediated by actions on pallidal DA. Consistent with this notion, cocaine altered oscillations in GP firing rates (Ruskin et al., 2001) and amphetamine changed GP neuronal activity after systemic (Bergstrom and Walters, 1981) or microiontophoretic injection (Czurko et al., 1995). Likewise, the GP supports electrical self-stimulation in rats, though less prominently as the ventral pallidum (Panagis et al., 1995). Furthermore, the GP is an integral part of the

cortical - dorsal striatopallidal circuit which has been implicated in habitual responding to psychostimulant drugs (Everitt and Wolf, 2002).

### 4.4. Conclusions

The pallidal DA innervation is brought about by collaterals of the nigrostriatal pathway (Lindvall and Bjorklund, 1979). Nigrostriatal axons show different arborisation patterns: Most axons project directly to the CPu, where they branched abundantly. Other axons arborised profusely in extrastriatal structures, including the GP, but branched only sparsely in the CPu. This heterogeneous organization of the nigrostriatal projection might allow a subset of nigral neurons to act directly upon the GP via a highly patterned set of collaterals (Gauthier et al., 1999), in particular as nigropallidal DA fibers – at least in primates – are segregated to some extent from the nigrostriatal system (Smith and Kieval, 2000). In neurochemical terms, our data do not support functional differences between pallidal and striatal DA input as physiological and pharmacological stimuli tested here elevated DA levels in the GP in a similar way as in the CPu (e.g. Feenstra, 2000). Nevertheless, the fact that pallidal DA release is responsive to an appetitive and an aversive stimulus indicates that DA signalling in the GP could play a role in control of behaviour governed by salient stimuli. Moreover, given the prominent stimulatory effects of D-amphetamine and cocaine on dialysate DA, our data suggest that DA in the GP is involved in mediating behavioural effects of psychostimulant drugs.

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