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ORIGINAL INVESTIGATION

A systematic microdialysis study of dopamine transmission in the accumbens shell/core and prefrontal cortex after acute antipsychotics

Gianluigi Tanda · Valentina Valentini · Maria Antonietta De Luca · Valentina Perra · Gian Pietro Serra · Gaetano Di Chiara

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Abstract
Rationale The only systematic in vivo studies comparing antipsychotic (AP) effects on nucleus accumbens (NAc) shell and core dopamine (DA) transmission are voltammetric studies performed in pargyline-pretreated, halothane-anaesthetized rats. Studies in freely moving rats not pretreated with pargyline are not available. This study was intended to fill this gap by the use of in vivo microdialysis in freely moving rats.
Methods Male Sprague-Dawley rats were implanted with microdialysis probes in the NAc shell and core and medial prefrontal cortex (PFCX). The next day, rats were administered intravenously with two or three doses of APs, and dialysate DA was monitored in 10-min samples. Some rats were pretreated with pargyline (75 mg/kg i.p.) and after 1 h were given clozapine or risperidone.
Results Clozapine, risperidone, quetiapine, raclopride, sulpiride and amisulpride increased DA preferentially in the NAc shell. Such preferential effect on shell DA was not observed after haloperidol, chlorpromazine and olanzapine. In contrast to voltammetric studies, a preferential effect on NAc core DA was not observed after any dose of AP. Pargyline pretreatment did not reduce but actually amplified the preferential effect of clozapine and risperidone on NAc shell DA.
Conclusions Apart from raclopride and olanzapine, the APs with lower extrapyramidal effects could be distinguished from typical APs on the basis of their ability to preferentially stimulate DA transmission in the NAc shell. There was no relationship between stimulation of PFCX DA and atypical APs profile. The differences between this study and voltammetry studies were not attributable to pargyline pretreatment.

Keywords Dopamine · Microdialysis · Accumbens shell · Accumbens core · Prefrontal cortex · Second-generation antipsychotics

Gianluigi Tanda and Valentina Valentini contributed equally to this work.

G. Tanda · V. Valentini · M. A. De Luca · V. Perra · G. P. Serra · G. Di Chiara (✉)
Department of Biomedical Sciences, Section of Neuropsychopharmacology, University of Cagliari, Via Ospedale 72, 09124 Cagliari, Italy
e-mail: dichiara@unica.it

V. Valentini · G. Di Chiara
Centre of Excellence "Neurobiology of Addiction", University of Cagliari, Cagliari, Italy

V. Valentini · M. A. De Luca · G. Di Chiara
National Institute of Neuroscience (INN), University of Cagliari, Cagliari, Italy

G. Di Chiara
Neuroscience Institute, Cagliari Section, National Research Council of Italy, Cagliari, Italy

Present Address:
G. Tanda
Medication Development Program, National Institute on Drug Abuse/Intramural Research Program/National Institutes of Health/ Department of Health and Human Services, Baltimore, MD, USA

Introduction

In spite of the vast number of studies made in the attempt to identify a unitary mechanism for the lower extrapyramidal symptom (EPS) liability of clozapine and second-generation antipsychotics (APs), no consensus has been reached (Abi-Dargham and Laruelle 2005; Arnt and Skarsfeldt 1998; Ginovart and Kapur 2012; Meltzer 1991). Thus, after a period of hot debate, the field has undergone a phase of resigned agnosticism. What is clear is that, depending on the specific AP, different mechanisms might concur to a low EPS profile. Among pharmacodynamic mechanisms are fast off-rate of

binding to D2 receptors (Kapur and Seeman 2001) and interactions with non-dopamine (DA) receptors (e.g. 5HT2A, alpha2 adrenergic, muscarinic receptors) (Arnt and Skarsfeldt 1998; Meltzer 1991). Among pharmacokinetic mechanisms is the slow rate of transfer into the brain by simple diffusion and carrier-mediated efflux out of the brain (e.g. P-glycoprotein) (Hartter et al. 2003; Linnet and Ejsing 2008).

Since the seminal studies by Carlsson (1974) (Carlsson and Lindqvist 1963), APs are known to increase all presynaptic indices of DA transmission, including synthesis, metabolism and release of DA and DA neuron firing activity (Anden et al. 1970; Bunney 1988; Imperato and Di Chiara 1985).

Along this line, an early explanation of the low EPS liability of clozapine is that of a "limbic specificity", i.e. the ability of activating DA turnover preferentially in the nucleus accumbens (NAc) as compared to the dorsal striatum (Anden and Stock 1973; Bartholini 1976; White and Wang 1983).

The NAc, however, is a heterogeneous area and has been distinguished into a ventromedial shell and a dorsolateral core that differ in terms of neurochemical composition, input and output connections, physiological and pharmacological responses and behavioural functions (Deutch and Cameron 1992; Di Chiara 2002; Heimer et al. 1997; Zahm 2000).

Clozapine and most second-generation antipsychotics stimulate to a larger extent Fos-like immunoreactivity in the NAc shell than in the dorsolateral striatum and in the core, while the opposite applies to first-generation APs (Deutch et al. 1992; Dilts et al. 1993; Robertson and Fibiger 1992). Another property of APs like clozapine, risperidone and olanzapine that block 5HT2A receptors is the ability to increase extracellular DA in the medial prefrontal cortex (PFCX) (Ichikawa et al. 1998, 2001; Imperato and Angelucci 1989; Kuroki et al. 1999; Moghaddam and Bunney 1990). This property has been related to their low EPS liability and/or the ability to control negative symptoms (Abi-Dargham et al. 2002; Knable and Weinberger 1997).

In spite of the interest of a shell vs core dichotomy for the action of APs, the only available comparative studies on the acute in vivo effects of APs on extracellular DA in the NAc shell and core are those of Marcus et al. (1996, 2000, 2002) and Franberg et al. (2008) who utilized differential normal pulse voltammetry in halothane-anaesthetized rats pretreated with pargyline, in order to avoid the interfering influence of DOPAC. It is notable that, in the same studies, brain microdialysis was utilized to monitor extracellular DA in the whole NAc, without distinguishing between shell and core. This is also the case of the studies by Volonte et al. (1997) and Kuroki et al. (1999). The only exception is the study by Shilliam and Dawson (2005) dealing exclusively with clozapine.

Therefore, no systematic in vivo study in freely moving rats not pretreated with pargyline is available. In order to fill this gap, we decided to embark in a systematic comparative microdialysis study of the acute effects of AP on extracellular DA in the NAc shell and core and medial prefrontal cortex (PFCX). Such a study might have predictive translational value, due to the high degree of concordance between microdialysis and PET as a means to monitor extracellular DA dynamics in specific brain areas (Morris et al. 2008; Narendran et al. 2014).

AP representative of different pharmacological categories were selected, namely haloperidol and chlorpromazine (high to intermediate D2R affinity and EPS liability), clozapine and quetiapine (low D2R, high to intermediate 5HT2A affinity and low EPS liability), amperozide (high 5HT2A, low D2R affinity and weak AP activity), risperidone and olanzapine (high D2R and 5HT2A affinity and mild EPS liability), raclopride (a benzamide with high D2R affinity, fast plasma-brain equilibration and high EPS liability) and, finally, (*S*)-sulpiride and amisulpride (benzamides with high D2R affinity, slow plasma-brain equilibration and low EPS liability) (Cassano et al. 1975; Csernansky et al. 1994; Harnryd et al. 1984; Leucht et al. 2013; Mauri et al. 1996; Rummel-Kluge 2010).

Methods and materials

Animals Male Sprague-Dawley rats (Harlan Laboratories, Italy) weighing 250 to 275 g at arrival in the animal facility were kept under standard conditions of temperature and humidity, in an artificial light dark cycle (light on 08.00 a.m., off 08.00 p.m.) and were housed six per cage (cage size, 40×70×20 cm) for at least 1 week before microdialysis surgery procedures. They had free access to food and water, except during microdialysis testing procedures. All procedures and experiments were carried out in an animal facility according to Italian (D.L. 116/92 and 152/06) and European Council directives (609/86 and 63/2010) and in compliance with the approved animal policies by the Ethical Committee for Animal Experiments (CESA, University of Cagliari) and the Italian Department of Health.

Probe preparation Concentric dialysis probes (dialysing portion 1.5 mm for NAc and 3.0 mm for PFCX) were prepared with AN69 fibres (310 μm o.d., 220 μm i.d., Gambro Hospal, Italy) by a modification of the method described by Tanda and Di Chiara (1998).

Surgery Rats were anaesthetized with Equitesin (2.5 mg/kg i.p.), placed in a stereotaxic apparatus and implanted with two dialysis probes aimed at the NAc shell on one side and at the NAc core or at the PFCX on the other side, according to the rat brain atlas of Paxinos and Watson (1998) (uncorrected coordinates: PFCX, anterior=+3.5, L=±0.6, from bregma; vertical=5.0 from dura; NAc shell, A=+2.0, L=0.9, V=8.0; NAc core, A=+1.6, L=1.5, V=7.6).

In order to perform intravenously (i.v.) drug administration, a catheter (Silastic, Dow Corning Corporation, Michigan, USA) was inserted in the right jugular vein according to the technique previously described (Lecca et al. 2006).

Microdialysis Experiments were performed 24 h after probe implant on freely moving rats. Ringer's solution (147.0 mM NaCl, 2.2 mM $CaCl_2$ and 4.0 mM KCl) was pumped through the dialysis probes at a constant rate of 1 μl/min. Collection of samples started after 30 min. After stabilization of dialysate DA (i.e. after about 1 h), rats were administered with drugs or saline.

Analytical procedure Dialysate samples (10 μl) were taken every 10 min and injected without purification into an HPLC apparatus equipped with a reverse-phase column (C8 3.5 μm, Waters, Mildford Massachusetts) and a coulometric detector (ESA Coulochem II, Bedford, MA) to quantify DA. The oxidation and reduction electrodes of the analytical cell (5014B, ESA, Bedford, MA) were set at + 130 mV and −175 mV, respectively. The mobile phase, containing 50 mM NaH_2PO_4, 0.1 mM Na_2EDTA, 0.5 mM *n*-octyl sulfate and 15 % (*v*/*v*) methanol (pH adjusted to 5.5 with Na_2HPO_4), was pumped with a Jasco pump at 1.0 ml/min. Assay sensitivity for DA was 5 fmol per sample.

Histology At the end of the experiment, rats were transcardially perfused with 100 ml saline and 500 ml of 4 % formaldehyde, 1 % calcium acetate and 100 mM NaCl solution. Probes were removed, and brains were cut on a vibratome in serial coronal slices oriented according to the atlas Paxinos and Watson (Paxinos and Watson 1998). Sections were processed in order to identify the location of the probes in relation to the PFCX and shell and core subdivisions of the NAc (Fig. 1).

Drugs Haloperidol, chlorpromazine, olanzapine, sulpiride (obtained from commercial sources), amperozide hydrochloride (Tocris Bioscience, UK), risperidone and pargyline hydrochloride (Sigma-Aldrich, Italy) were dissolved in 0.9 % NaCl. Clozapine and amisulpride (Tocris Bioscience, UK), raclopride (Sigma-Aldrich, Italy) and quetiapine (kindly provided by Astra Zeneca) were all dissolved in a minimal amount of acetic acid and 0.9 % NaCl buffered to pH 7.4 with 1 N NaOH.

All drugs were administered i.v. except for pargyline that was given i.p. Drug doses were selected on the basis of the results of previous studies from our laboratory (Imperato and Di Chiara 1985) and of pilot experiments intended to identify the threshold dose for maximal increase of dialysate DA (that for APs corresponds to twice the basal values) in the most sensitive area of the accumbens (either shell or core). Once this dose was identified, a lower, and in some cases, a higher dose, was also studied. The higher dose level of clozapine and risperidone was taken from the study by Marcus et al. (1996) in order to compare the effect of these drugs in control and pargyline-pretreated rats. In the case of amperozide, we selected a dose about seven times higher, on a milligramme per kilogramme basis, than the total daily dose (20 mg) utilized in the study by Axelsson et al. (1991).

Three dose levels (in mg/kg) were studied for haloperidol (0.006, 0.0125, 0.025), clozapine (1.0, 2.0, 5.0), olanzapine (0.125, 0.25, 0.50), risperidone (0.05, 0.1, 1.0), quetiapine (2.5, 5.0, 20.0) and amisulpride (1.0, 2.0, 4.0). Two dose levels were studied for chlorpromazine (0.25, 0.5), raclopride (0.025, 0.075), sulpiride (10.0, 18.0) and amperozide (1.0, 2.0). A posteriori, taking into account that in the present study drugs were given i.v., the range of doses selected compares favourably, on a milligramme per kilogramme basis, with

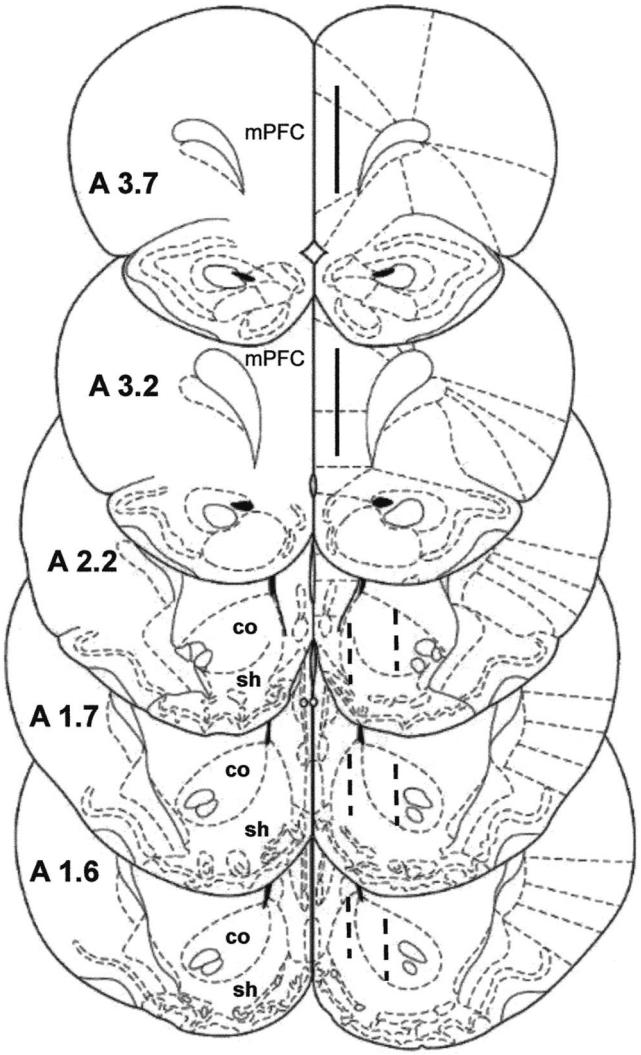

Fig. 1 Schematic localization of microdialysis probe dialysing portion within the PFCX, the NAc shell (*sh*) and core (*co*) according to Paxinos and Watson (1998)

individual doses of intramuscular and oral APs utilized in the clinic (Gardner et al. 2010).

Statistics Three-way repeated measures ANOVA with brain area, drug dose (vehicle and two or three doses, depending on the group) and time as factors were applied to the data obtained from serial assays of DA. Four-way ANOVA (factors: area, pretreatment, treatment) for repeated measures over time was carried out for the analysis of data obtained from pargyline experiments. For graphical purposes, data were normalized as percentage of basal DA values. For clarity, vehicle time course has been omitted from the figures but was included in the analysis. Basal DA values were means of three consecutive samples differing no more than 10 %. Results from treatments showing overall changes were subjected to post hoc Tukey's test with significance at $p<0.05$.

Results

Basal dialysate dopamine

Basal values of DA (fmoles/10 min sample±SEM) in the three brain areas under study were PFCX, 9.6±1.3 ($N=146$); NAc shell, 48.6±7.8 ($N=168$); and NAc core, 53.5±8.5 ($N=164$).

No significant differences between treatment groups were found for each brain area.

Effect of antipsychotics on NAc shell and core and prefrontal cortex dopamine

Haloperidol (6.0, 12.5 and 25.0 μg/kg) dose-dependently increased dialysate DA in the NAc shell and core and to a lesser extent in the PFCX (Fig. 2). The time course of shell DA after 12.5 and 25.0 μg/kg was biphasic with a peak followed by a lower shoulder. In the core, no initial peak but only a progressive increase to a plateau was observed. Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(3,40)}=82.33$; $p<0.001$], area [$F_{(2,40)}=29.25$; $p<0.001$] and time [$F_{(18,720)}=14.59$, $p<0.001$] and an interaction of area × dose [$F_{(6,40)}=4.78$, $p<0.001$], area × time [$F_{(36,720)}=2.88$; $p<0.001$] and dose × time [$F_{(54,720)}=3.76$; $p<0.001$]. Post hoc analysis showed that haloperidol increased dialysate DA to a greater extent in the NAc shell and core than in the PFCX without differences between shell and core. Analysis of NAc shell and core data alone for all the doses by three-way ANOVA or for each dose of haloperidol also failed to reveal post hoc differences between shell and core.

Chlorpromazine(0.25 and 0.5 mg/kg), like haloperidol, dose-dependently increased dialysate DA in the NAc shell, in the core and to a lesser extent, in the PFCX (Fig. 3). The time course of the effect of 0.5 mg/kg chlorpromazine on shell DA was characterized, like that of haloperidol, by a sharp peak followed by a shoulder. In contrast, after the same dose, DA increased in the core to a plateau without an initial peak. Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,27)}=58.40$, $p<0.001$], area [$F_{(2,27)}=11.64$; $p<0.001$] and time [$F_{(18,486)}=36.56$, $p<0.001$] and an interaction of area × dose [$F_{(4,27)}=3.31$, $p<0.05$], area × time [$F_{(36,486)}=5.83$, $p<0.001$], dose × time [$F_{(36,486)}=11.49$, $p<0.001$] and area × dose × time [$F_{(72,486)}=2.89$, $p<0.001$]. Post hoc analysis showed a larger increase of dialysate DA in the NAc shell and in the core as compared to the PFCX but no differences between shell and core. No differences on post hoc test were obtained by three-way ANOVA of the shell and core data alone for all the doses or for each dose of chlorpromazine.

Raclopride (25 and 75 μg/kg) increased dialysate DA in the NAc shell and to a lesser extent in the core and in the PFCX (Fig. 4). The time course of raclopride effect in the shell consisted of a sharp increase peaking 20–30 min post-drug. Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,30)}=32.27$, $p<0.001$], area [$F_{(2,30)}=8.98$, $p<0.001$] and time [$F_{(18,540)}=67.01$, $p<0.001$] and an interaction of area × dose [$F_{(4,30)}=7.97$, $p<0.001$], area × time [$F_{(36,540)}=7.94$, $p<0.001$], dose × time [$F_{(36,540)}=16.72$, $p<0.001$] and area × dose × time [$F_{(72,540)}=3.19$, $p<0.001$]. Post hoc analysis showed that raclopride induced a greater increase of dialysate DA in the shell as compared to the core and PFCX.

Clozapine (1.0 and 2.0 mg/kg) increased dialysate DA in the PFCX to a larger extent than in the NAc shell but not in the core (Fig. 5). Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,33)}=23.98$, $p<0.001$], area [$F_{(2,33)}=26.96$, $p<0.001$] and time [$F_{(18,594)}=56.87$, $p<0.001$] and an interaction of area × dose [$F_{(4,33)}=6.94$, $p<0.001$], area × time [$F_{(36,594)}=17.38$, $p<0.001$], dose × time [$F_{(36,594)}=18.34$, $p<0.001$] and area × dose × time [$F_{(72,594)}=5.00$, $p<0.001$]. Post hoc analysis showed that clozapine elicited a greater increase of dialysate DA in the PFCX as compared to the shell and core. Three-way ANOVA and post hoc test on the NAc shell and core data showed that clozapine elicited a greater increase of dialysate DA in the shell as compared to the core [$F_{(1,25)}=47.36$, $p<0.001$].

Risperidone (50 and 100 μg/kg) increased dialysate DA in the PFCX more than in the NAc shell and core and more in the shell as compared to the core after the higher dose (Fig. 6). The time course of DA showed an early peak in the shell and a plateau in the core after the lower dose. Saline administration

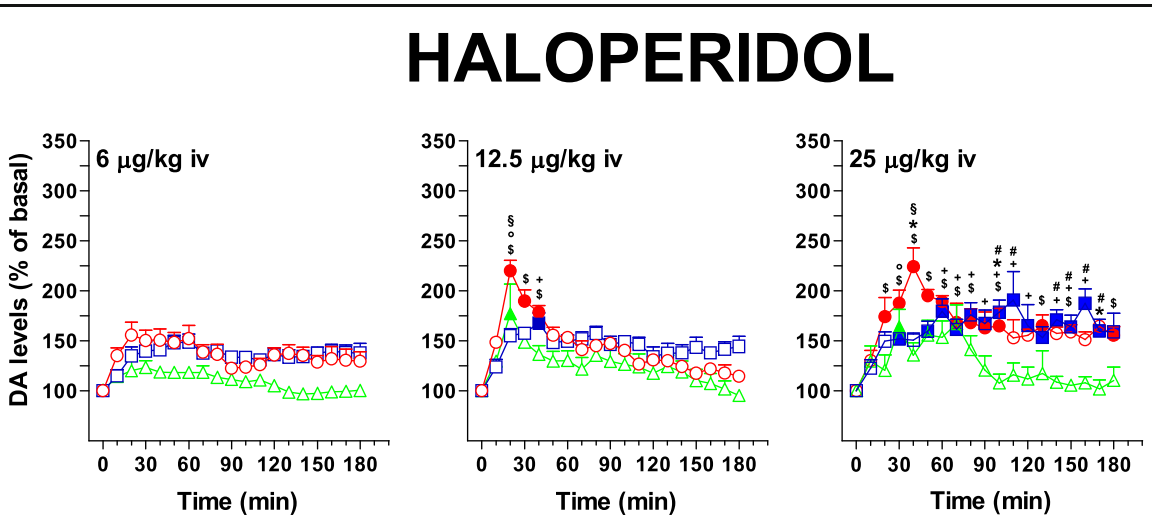

Fig. 2 Effect of haloperidol (6, 12.5 and 25 µg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=17$; NAc core, $N=18$; PFCX, $N=17$)

in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,30)}=127.20$, $p<0.001$], area [$F_{(2,30)}=22.71$, $p<0.001$] and time [$F_{(18,540)}=83.57$, $p<0.001$] and an interaction of area × dose [$F_{(4,30)}=10.43$, $p<0.001$], area × time [$F_{(36,540)}=9.60$, $p<0.001$], dose × time [$F_{(36,540)}=22.00$, $p<0.001$] and area × dose × time [$F_{(72,\ 540)}=3.60$, $p<0.001$]. Post hoc test showed that risperidone induced a greater increase of dialysate DA in the PFCX as compared to the shell and core and a greater increase of dialysate DA in the shell as compared to the core.

Olanzapine (0.125, 0.25 and 0.5 mg/kg) increased dialysate DA in the PFCX to a greater extent than in the shell and core, but no differences were obtained between shell and core (Fig. 7). The time course of DA showed an early peak in the shell and a plateau in the core after the intermediate dose tested. Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(3,38)}=79.41$, $p<0.001$], area [$F_{(2,38)}=18.81$, $p<0.001$] and time [$F_{(18,684)}=111.91$, $p<0.001$] and an interaction of area × dose [$F_{(6,38)}=3.96$, $p<0.001$], area × time [$F_{(36,684)}=16.8$, $p<0.001$], dose × time [$F_{(54,684)}=16.1$, $p<0.001$] and area × dose × time [$F_{(108,684)}=5.87$, $p<0.001$]. Post hoc analysis showed that olanzapine increased to a greater extent dialysate DA in the PFCX as compared to the shell and core of the NAc,

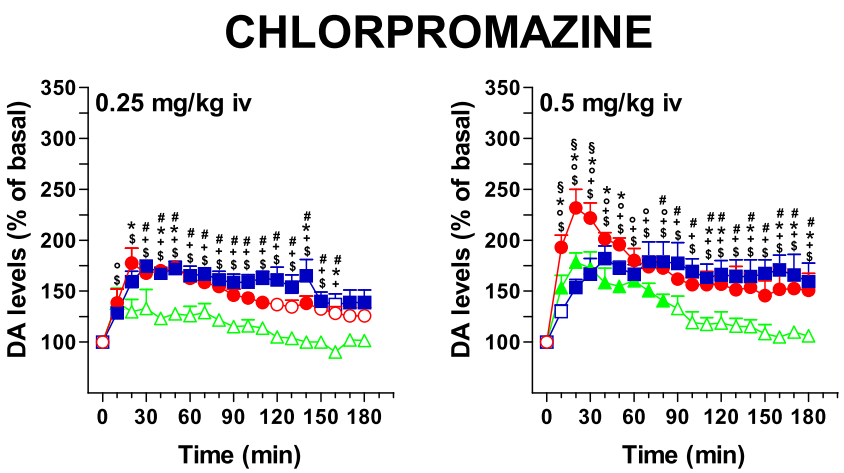

Fig. 3 Effect of chlorpromazine (0.25 and 0.5 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core *vs* the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=12$; NAc core, $N=12$; PFCX, $N=12$)

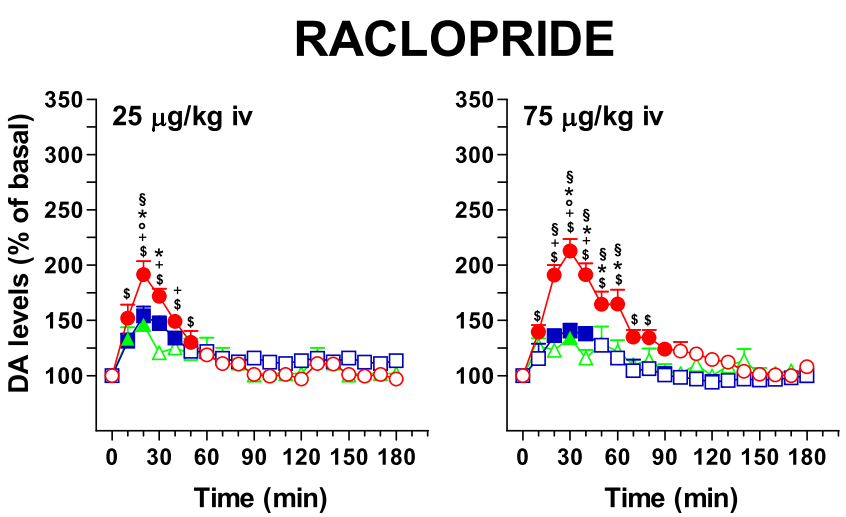

Fig. 4 Effect of raclopride (25 and 75 µg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=13$; NAc core, $N=13$; PFCX, $N=13$)

but no differences were obtained between shell and core. Analysis of NAc shell and core data alone for all the doses by three-way ANOVA or for each dose of olanzapine also failed to reveal post hoc differences between shell and core (Fig. 7).

Quetiapine (2.5, 5.0 and 20.0 mg/kg) increased dialysate DA in the NAc shell but not in the core. DA increased in the PFCX only after the highest dose (Fig. 8). Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(3,51)}=23.36$, $p<0.001$] and time [$F_{(18,918)}=21.16$, $p<0.001$] and an interaction of area × dose [$F_{(6,51)}=2.78$, $p<0.05$], area × time [$F_{(36,918)}=1.97$, $p<0.001$] and dose × time [$F_{(54,918)}=4.61$, $p<0.01$]. Three-way ANOVA of only shell and core values showed that quetiapine elicited a greater increase of dialysate DA in the shell as compared to the core [$F_{(1,31)}=4.65$, $p<0.05$].

Amisulpride (1.0, 2.0 and 4.0 mg/kg) slowly and lastingly increased dialysate DA in the NAc shell and core but not in the PFCX (Fig. 9), and this effect was more pronounced in the shell than in the core. Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(3,51)}=13.8$, $p<0.0001$], area [$F_{(2,51)}=43.74$,

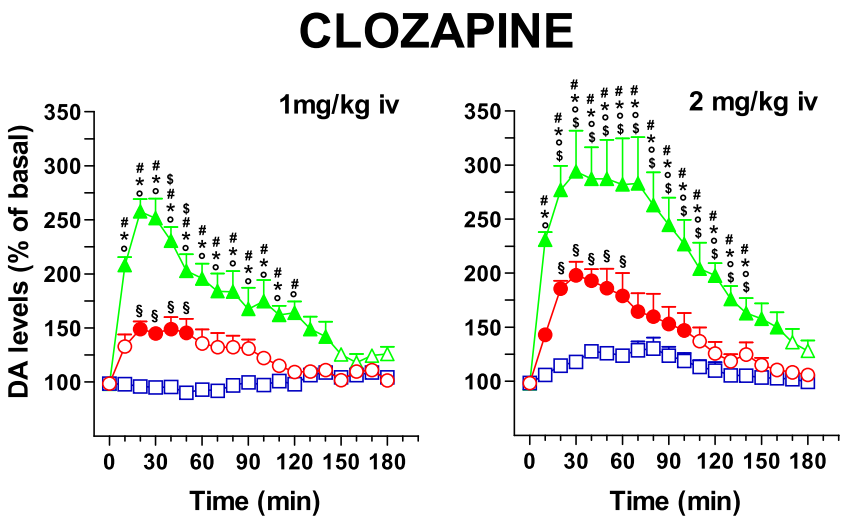

Fig. 5 Effect of clozapine (1 and 2 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=14$; NAc core, $N=13$; PFCX, $N=15$)

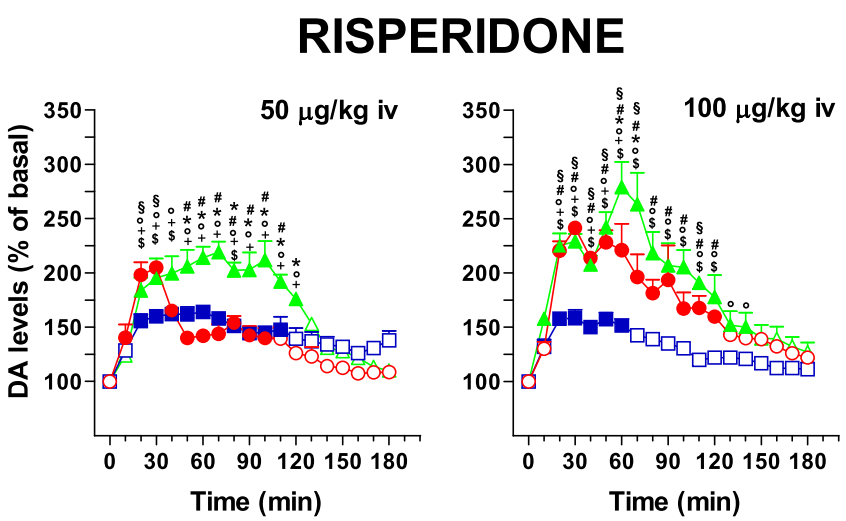

Fig. 6 Effect of risperidone (50 or 100 μg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=13$; NAc core, $N=13$; PFCX, $N=13$)

$p<0.0001$] and time [$F_{(24,1224)}=7.63$, $p<0.0001$] and an interaction of area × dose [$F_{(6,51)}=8.01$, $p<0.0001$], area × time [$F_{(48,1224)}=8.99$, $p<0.0001$], dose × time [$F_{(72,1224)}=1.90$, $p<0.0001$] and area × dose × time [$F_{(144,1224)}=1.92$, $p<0.0001$]. Post hoc analysis showed that amisulpride elicited a greater stimulation of dialysate DA in the NAc shell and core as compared to the PFCX.

(*S*)-*sulpiride* (10 and 18 mg/kg) elicited a slow and long-lasting increase of dialysate DA in the NAc shell and core but not in the PFCX (Fig. 10). Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,30)}=18.76$, $p<0.001$], area [$F_{(2,30)}=13.85$, $p<0.01$] and time [$F_{(24,720)}=9.70$, $p<0.001$] and an interaction of area × dose [$F_{(4,30)}=4.58$, $p<0.01$], area × time [$F_{(48,720)}=2.51$, $p<0.001$] and dose × time [$F_{(48,720)}=3.47$, $p<0.001$]. Post hoc analysis showed that sulpiride increased to a larger extent dialysate DA in the NAc shell and core as compared to the PFCX, but no differences were observed between shell and core. Three-way ANOVA and post hoc test of dialysate DA in the NAc shell and core confirmed the lack of shell vs core differences obtained in the analysis that included PFCX values. However, analysis of data for each dose showed that the highest dose of sulpiride elicited a greater increase of dialysate DA in the shell as compared to the core [$F_{(2,12)}=18.17$, $p<0.001$].

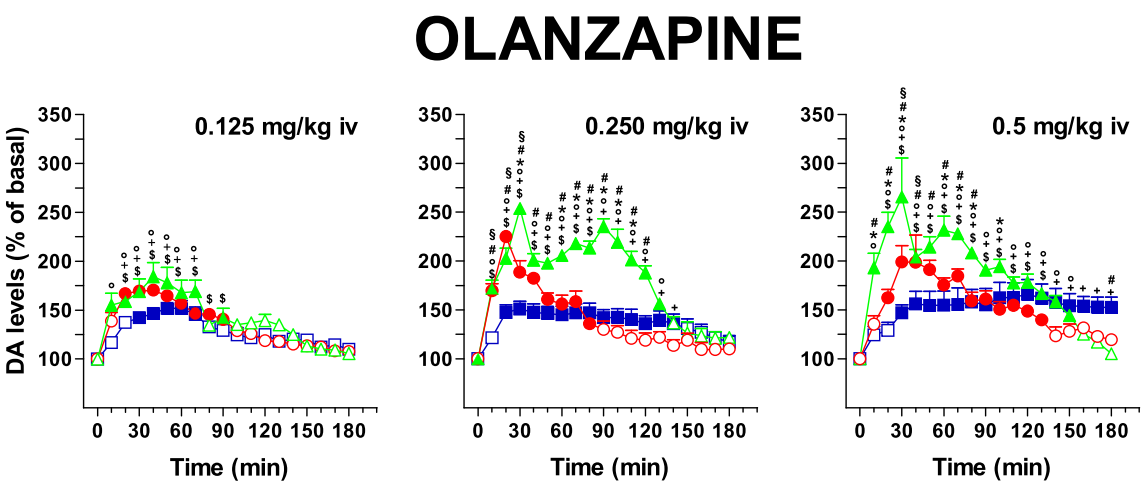

Fig. 7 Effect of olanzapine (0.125, 0.25 and 0.5 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group; and °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=17$; NAc core, $N=17$; PFCX, $N=16$)

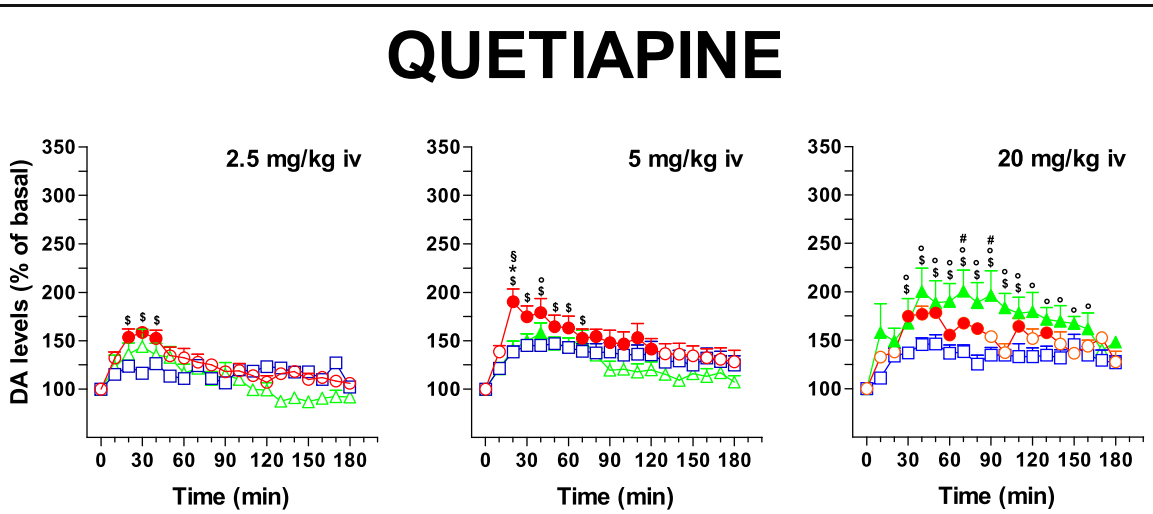

Fig. 8 Effect of quetiapine (2.5, 5.0 and 20.0 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; °$p<0.05$ PFCX vs the corresponding time point of saline group (NAc shell, $N=21$; NAc core, $N=19$; PFCX, $N=27$)

Amperozide (1.0 and 2.0 mg/kg) increased dialysate DA in the PFCX but not in the NAc shell and core (Fig. 11). Saline administration in control group did not modify dialysate DA in the PFCX, shell and core (data not shown). Three-way ANOVA revealed a main effect of dose [$F_{(2,27)}=58.31$, $p<0.001$], area [$F_{(2,27)}=72.39$, $p<0.001$] and time [$F_{(18,486)}=41.00$, $p<0.001$] and an interaction of area × dose [$F_{(4,27)}=38.41$, $p<0.001$], area × time [$F_{(36,486)}=29.73$, $p<0.001$], dose × time [$F_{(36,486)}=16.83$, $p<0.001$] and area × dose × time [$F_{(72,\ 486)}=15.80$, $p<0.001$]. Post hoc analysis showed that amperozide increased to a greater extent dialysate DA in the PFCX as compared to the shell and core of the NAc.

Effects of pargyline pretreatment on the effect of clozapine and risperidone on NAc shell and core dopamine

Pargyline (75 mg/kg i.p.) increased dialysate DA in shell and core to about 280 % (data not shown). Pretreatment with pargyline 1 h before clozapine (5 mg/kg, Fig. 12a) and risperidone (1 mg/kg, Fig. 12b) strongly potentiated the increase of dialysate DA induced in normal animals. In rats pretreated with pargyline, the increase of DA in the shell vs core was larger than that observed in normal rats. In Fig. 12a, four-way ANOVA revealed a main effect of pretreatment (saline or pargyline) [$F_{(1,23)}=102.01$, $p<0.001$], treatment (saline or clozapine) [$F_{(1,23)}=72.93$, $p<0.001$], area [$F_{(1,23)}=177.33$,

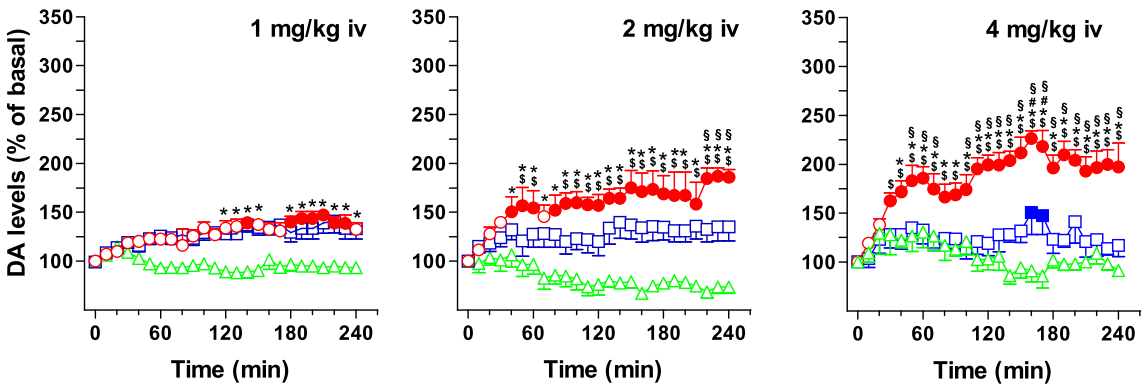

Fig. 9 Effect of amisulpride (1, 2.0 and 4.0 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group (NAc shell, $N=21$; NAc core, $N=20$; PFCX, $N=21$)

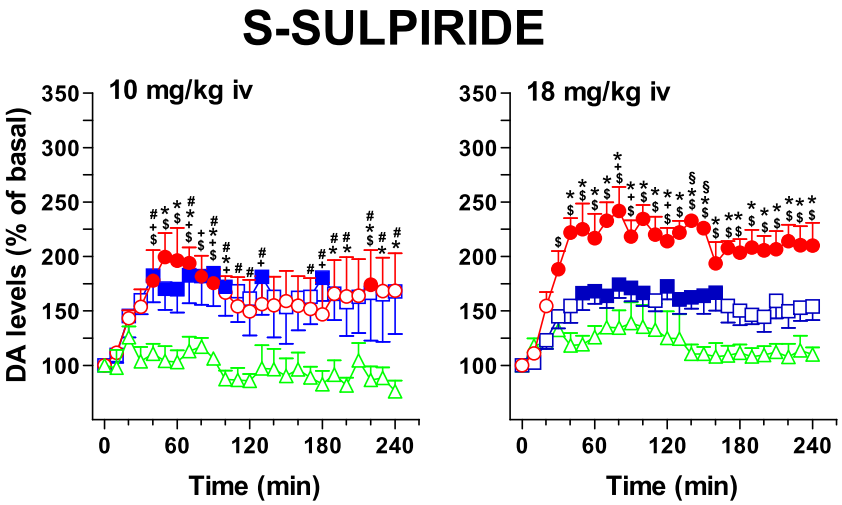

Fig. 10 Effect of (*S*)-sulpiride (10 and 18.0 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; §$p<0.05$ NAc shell vs NAc core; $$p<0.05$ NAc shell vs the corresponding time point of saline group; +$p<0.05$ NAc core vs the corresponding time point of saline group (NAc shell, $N=15$; NAc core, $N=14$; PFCX, $N=20$)

$p<0.01$] and time [$F_{(18,414)}=31.828$, $p<0.001$] and an interaction of pretreatment × treatment × area [$F_{(1,23)}=23.69$, $p<0.001$] and pretreatment × treatment × area × time [$F_{(18,414)}=1.62$, $p<0.05$]. Post hoc analysis showed that pargyline potentiated clozapine effect in the NAc shell and core, and this effect was higher in the shell vs core. In Fig. 12a four-way ANOVA revealed a main effect of pretreatment (saline or pargyline) [$F_{(1,26)}=14.27$, $p<0.001$], treatment (saline or risperidone) [$F_{(1,26)}=27.45$, $p<0.001$], area [$F_{(1,26)}=4.54$, $p<0.05$] and time [$F_{(18,468)}=12.62$, $p<0.001$] and an interaction of area × treatment [$F_{(1,26)}=4.5$, $p<0.05$], treatment × time [$F_{(18,468)}=10.12$, $p<0.001$], pretreatment × treatment × time [$F_{(18,468)}=4.21$, $p<0.01$] and area × treatment × time [$F_{(18,468)}=2.88$, $p<0.01$]. Post hoc analysis showed that pargyline potentiated risperidone effect in the NAc shell but not in the core.

Discussion

The present report is, to our knowledge, the first systematic comparative microdialysis study of the acute effect of APs on extracellular DA in NAc shell and core and medial PFCX of freely moving rats. Clozapine, quetiapine, risperidone, sulpiride, amisulpride and raclopride increased, at least at one dose level, dialysate DA preferentially in the shell vs core while haloperidol, chlorpromazine and olanzapine failed to do so at any dose tested. Clozapine, risperidone, quetiapine and olanzapine increased DA also in the PFCX, but this property was not always associated to a preferential DA increase in the shell, as sulpiride and amisulpride did not show it.

All APs, with the exception of sulpiride and amisulpride, showed a prominent shell DA peak on the first hour post-drug, followed by a shoulder. No DA peak, but a progressive

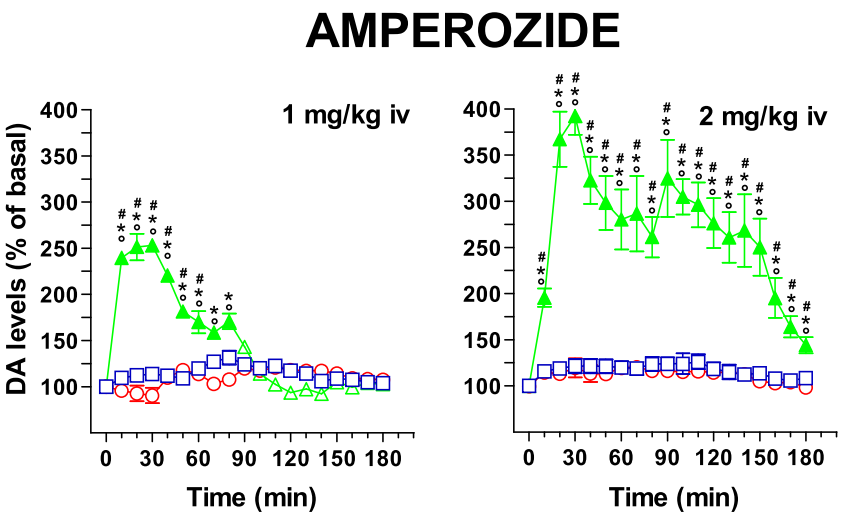

Fig. 11 Effect of amperozide (1.0 and 2.0 mg/kg i.v.; saline not shown) on NAc shell (*circles*), NAc core (*squares*) and PFCX (*triangles*) dialysate DA. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. *Solid symbols*: $p<0.05$ vs the respective basal values; *$p<0.05$ NAc shell vs PFCX; #$p<0.05$ NAc core vs PFCX;°$p<0.05$ PFCX *vs* the corresponding time point of saline group (NAc shell, $N=12$; NAc core, $N=12$; PFCX, $N=12$)

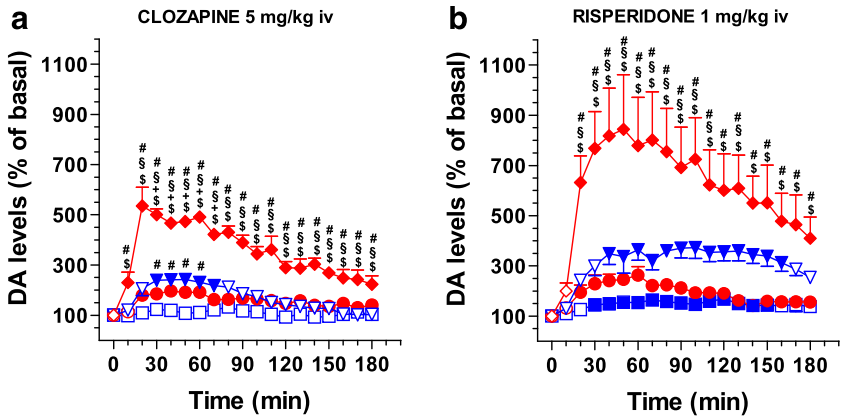

Fig. 12 Effect of 1-h pretreatment with pargyline (75 mg/kg i.p.) on **a** clozapine- (5 mg/kg iv; saline not shown) or **b** risperidone- (1 mg/kg iv; saline not shown) induced dialysate DA increase in the NAc shell and core. *Diamond* and *triangle*: shell and core of pargyline-pretreated groups, respectively; *circle* and *square*: shell and core of saline-pretreated groups, respectively. Results are expressed as mean±SEM of dialysate DA levels expressed as percentage of basal values. In pargyline-pretreated rats, basal values correspond to the mean of the last three samples of 1-h pargyline pretreatment. *Solid symbols*: $p<0.05$ vs the respective basal values. Referred to pargyline-pretreated groups, $§$ $p<0.05$ NAc shell vs NAc core; $\$p<0.05$ NAc shell vs the corresponding time point of saline group; $+p<0.05$ NAc core vs the corresponding time point of saline group; $\#p<0.05$ vs the corresponding saline-pretreated group. (**a** NAc shell, $N=16$; NAc core, $N=15$; **b** NAc shell, $N=17$; NAc core, $N=18$)

increase to a plateau, was observed in the core. The early shell DA peak would result from fast distribution of lipophilic AP to the highly perfused brain compartment (Balant-Gorgia and Balant 1987; Byerly and DeVane 1996; Jann et al. 1993; Javaid 1994; Johnson et al. 2011; Nord and Farde 2011; Verghese et al. 1991). This interpretation is consistent with the observation that amisulpride and sulpiride, which slowly distribute to the brain, lack the initial peak (Mauri et al. 1996; Rosenzweig et al. 2002).

The reason for such a different temporal profile of the response of dialysate DA to APs in the shell and in the core might derive in part from different DA dynamics related to a more efficient DA uptake in the core. Due to this, changes in burst firing activity of DA neurons would induce larger changes in extracellular DA in the shell than in the core (Calipari et al. 2012; Jones et al. 1996; Wu et al. 2001).

Among the three areas investigated, the effect common to all antipsychotics was the ability to increase dialysate DA in the NAc shell, consistent with an important role of this effect in the action of APs.

Raclopride's preferential effect in the shell might be due to the short duration of action of this AP and to the rapid plasma/brain equilibration of its concentrations, generating a prominent early DA peak in the NAc that, given the short half-life of the drug, dominates the picture and drives the overall effect of the drug (see below).

The observation that APs that block 5HT2A receptors with high affinity preferentially increase dialysate DA in the shell might suggest that blockade of 5HT2A receptors specifically potentiates the stimulatory influence of D2 receptor blockade on DA release in the NAc shell. However, while Andersson et al. (1995) reported that ritanserin, a 5HT2A/2C antagonist, potentiates the DA stimulant properties of raclopride in the NAc, Liegeois et al. (2002) reported that ML100907, a selective 5HT2A antagonist, partially prevents the increase of dialysate DA induced by haloperidol in the NAc. However, both these studies did not differentiate shell from core in the NAc and therefore cannot be compared with our study.

The observation that sulpiride and amisulpride preferentially activate in vivo DA transmission in the shell was unexpected, in view of their high affinity and selectivity for D2 receptors that makes them quite different from clozapine. Although amisulpride has been reported to preferentially stimulate DA metabolism in the NAc as compared to the caudate-putamen, again no distinction has been made between shell and core (Schoemaker et al. 1997). These drugs being highly selective for D2 receptors, a pharmacodynamic mechanism for their preferential shell effect is unlikely. We would rather suggest a pharmacokinetic mechanism related to their slow accumulation into the brain.

As far as the voltammetric studies by Marcus et al. (1996, 2000, 2002) are concerned, many discrepancies are found. According to their studies, clozapine and risperidone increase DA preferentially in the shell after lower doses and in the core after higher doses. Instead, we consistently observed a selective (clozapine) or a preferential (risperidone) increase of DA in the shell. In general, we failed to observe a preferential increase of DA in the core even after haloperidol and chlorpromazine. These discrepancies cannot be accounted for by differences in the sensitivity of microdialysis vs voltammetry since results refer to relative (% of basal) rather than absolute differences between shell and core.

In order to shed light on this issue, we set to test the effect of clozapine and risperidone at the same doses utilized by

Marcus et al. (1996) in rats pretreated with pargyline. In contrast to Marcus et al. (1996), pargyline pretreatment did not induce a preferential core increase of extracellular DA but actually amplified the preferential effect on the shell induced by clozapine and risperidone in rats not pretreated with pargyline. These observations indicate that the discrepancies between our observations and those of Marcus et al. (2000, 2002) are not due to pargyline pretreatment but, eventually, to the voltammetric technique itself and/or to the use of anaesthetized instead of freely moving rats. Indeed halothane anaesthesia has been reported to reduce the increase of striatal dialysate DA induced by haloperidol and to increase that elicited by clozapine (Adachi et al. 2003) while fluothane anaesthesia has been reported to attenuate the effect of clozapine and risperidone (Adachi et al. 2008).

Amperozide is a case of its own and deserves a separate discussion. In our hands, amperozide, given i.v. at doses (on a mg/kg basis) about seven times the total daily oral dose given to patients in the study by Axelsson et al. (1991), failed to increase DA in dialysates from the NAc shell, in agreement with some reports (Hertel et al. 1996; Kuroki et al. 1999) but at variance with others (Ichikawa and Meltzer 1992, 2000; Marcus et al. 1996; Nomikos et al. 1994). However, in the present study, 2.0 mg/kg i.v. of amperozide increased to 400 % dialysate DA in the PFCX and at 6 mg/kg i.p. up to 300 % in the bed nucleus stria terminalis (Carboni et al. 2000). Amperozide is a weak D2 ligand but a strong 5HT2A receptor ligand (Svartengren and Simonsson 1990). Early reports suggested that amperozide had antipsychotic efficacy and low EPS (Axelsson et al. 1991). Subsequent clinical experience, however, did cast doubt on its effectiveness as an antipsychotic, leading to interruption of its development (Breier 1995). Thus, the amperozide case illustrates the relationship between the ability to increase DA in the NAc shell and the effectiveness of a drug as an AP.

APs increase NAc shell Fos-like immunoreactivity and this effect has been related to their antipsychotic activity (Robertson et al. 1994). Typical APs also increase Fos-like immunoreactivity in the dorsal caudate-putamen and this effect has been related to EPS liability (Robertson et al. 1994). In principle, stimulation of D1 receptors by DA released as a result of D2/D3 blockade might contribute to Fos-like immunoreactivity induced by APs. However, Fos activation in the dorsolateral striatum by typical APs is resistant to D1 blockade by SCH 23390 (Dragunow et al. 1990; Wirtshafter and Osborn 2005). No information is available on the effect of D1 blockade on Fos activation by APs in the NAc shell.

The stimulatory properties of APs on PFCX DA differentiate a class of APs, namely clozapine, risperidone, olanzapine and quetiapine, that, at clinically effective doses, blocks 5HT2A receptors. This observation, in turn, is consistent with previous studies (Ichikawa et al. 1998, 2001; Imperato and Angelucci 1989; Kuroki et al. 1999; Moghaddam and Bunney 1990). However, this effect is not a marker of low EPS liability as amisulpride and sulpiride, drugs without 5HT2A receptor affinity, do not increase PFCX DA. This observation suggests that blockade of 5HT2A receptors is not a prerequisite for low EPS liability.

The association of low EPS liability and preferential activation of NAc shell vs core DA transmission might be due to the fact that these two properties share some pharmacodynamic and pharmacokinetic determinants. During the initial phase of drug distribution, when most of the drug is still in the blood, highly lipophilic APs, like clozapine, quetiapine, haloperidol and chlorpromazine, rapidly equilibrate with the highly perfused brain compartment (Balant-Gorgia and Balant 1987; Byerly and DeVane 1996; Jann et al. 1993; Javaid 1994; Johnson et al. 2011; Nord and Farde 2011; Verghese et al. 1991). In this phase, distribution to the less perfused peripheral compartments has not yet taken place. As a result of this, APs with a slow k-off rate, as haloperidol and chlorpromazine (Kapur and Seeman 2001), would remain tightly bound to D2 receptors in spite of the subsequent decrease of brain drug levels, as distribution to peripheral compartments takes place. This long-lasting and high occupancy of NAc core D2 receptors would allow a steady activation of DA transmission in the core after peak DA activation, reflecting initial drug distribution, has taken place in the shell.

In the case of clozapine and quetiapine, fast dissociation (k-off) from D2 receptors (Kapur and Seeman 2001) would allow the reduction of receptor occupancy in parallel with the decrease of brain drug concentrations due to its distribution to peripheral compartments. Under these conditions, the level and duration of D2 receptor occupancy, while sufficient for fully increasing DA transmission in the shell, would not be sufficient for activating core DA.

Less lipophilic drugs like amisulpride and sulpiride, which slowly enter the brain (Mauri et al. 1996; Rosenzweig et al. 2002), or like risperidone, which is rapidly converted into the less liposoluble 9-hydroxy metabolite, paliperidone (Mannens et al. 1993; Muly et al. 2012), given in appropriate doses, increase DA preferentially in shell because the absence of the initial overshoot allows titration of the drug to doses that preferentially activate DA in the shell, an area with higher responsivity of DA transmission compared to the core due to a lower level of DA transporter (Calipari et al. 2012; Wu et al. 2001). However, once NAc shell DA has reached its maximal stimulation, higher doses would further increase DA in the core, with loss of preferential shell DA activation.

For two drugs, raclopride and olanzapine, the relationship of differential shell vs core pattern and EPS liability did not hold. Raclopride might be a false positive since its short action makes the initial DA shell peak to dominate the overall time course and result in a preferential shell pattern. Olanzapine, instead, might be a false negative, its low EPS liability being independent of a differential shell vs core pattern, but related

instead to its powerful in vivo antimuscarinic properties, superimposable to those of clozapine (Bymaster et al. 2003; Chew et al. 2006). In fact, olanzapine has nanomolar affinity for D2 receptors and rapid blood/brain equilibration that makes it more similar to chlorpromazine than to clozapine (Jones et al. 1996).

We therefore hypothesize that the shell/core differences in the responsiveness of DA transmission to APs are related to differences in the dynamics of DA and in the temporal and fractional scaling of D2 occupancy by APs necessary for shell vs core activation of DA transmission.

Although the relationship between shell vs core DA activation pattern and APs EPS liability can be understood as essentially indirect, being due to sharing of some common determinants, a more direct relationship can be envisioned. Thus, Shilliam and Dawson (2005) have reported that chronic exposure to clozapine results in reversal, from stimulation to inhibition, of its effect on dialysate shell DA. This reversal is not observed in the core. This pattern of change has been interpreted as due to depolarization inactivation of ventrotegmental area neurons projecting to the shell (Shilliam and Dawson 2005). Selective depolarization inactivation of DA neurons to the shell with sparing of DA neurons projecting to the neostriatum has been proposed as the basis for the low EPS liability of clozapine and second-generation antipsychotics (Chiodo and Bunney 1983; Grace et al. 1997). Therefore, the differential responsiveness of shell vs core DA transmission to acute APs might be the premise for depolarization inactivation of shell DA neurons and sparing of DA neurons to the core and dorsal caudate-putamen after chronic APs. If this is the case, the differential responsiveness of shell vs core DA might be relevant for AP therapeutic effectiveness and EPS liability. Chronic studies relating acute to chronic AP effects will be needed to clarify these issues.

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Conflict of interest Authors do not have any conflict of interest to declare.

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