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Functional Aspects of Dopamine Metabolism in the Putative Prefrontal Cortex Analogue and Striatum of Pigeons (*Columba livia*)

TOBIAS BAST,[1,2] BETTINA DIEKAMP,[1]* CHRISTIANE THIEL,[3] RAINER K.W. SCHWARTING,[3,4] AND ONUR GÜNTÜRKÜN[1]

[1]Biopsychologie, Fakultät für Psychologie, Ruhr-Universität Bochum, 44780 Bochum, Germany

[2]Laboratory of Behavioral Neurobiology, The Swiss Federal Institute of Technology Zurich, CH 8603 Schwerzenbach, Switzerland

[3]Institut für Physiologische Psychologie I und Biologisch-Medizinisches Forschungszentrum, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany

[4]Allgemeine und Physiologische Psychologie, Philipps-Universität Marburg, 35032 Marburg, Germany

ABSTRACT

Dopamine (DA) in mammalian associative structures, such as the prefrontal cortex (PFC), plays a prominent role in learning and memory processes, and its homeostasis differs from that of DA in the striatum, a sensorimotor region. The neostriatum caudolaterale (NCL) of birds resembles the mammalian PFC according to connectional, electrophysiological, and behavioral data. In the present study, DA regulation in the associative NCL and the striatal lobus parolfactorius (LPO) of pigeons was compared to uncover possible differences corresponding to those between mammalian PFC and striatum. Extracellular levels of DA and its metabolites (homovanillic acid [HVA], dihydroxyphenylacetic acid [DOPAC]) and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) were investigated by in vivo microdialysis of urethane-anesthetized pigeons under basal conditions and after systemic administration of D-amphetamine. DA was reliably determined only in LPO dialysates, and DA metabolite levels were significantly higher in LPO than in NCL. The HVA/DOPAC ratio, indicating extracellular lifetime of DA, was more than twice as high in NCL than in LPO dialysates. After amphetamine, DA increased in LPO while still being undetectable in NCL, and DA metabolites decreased in both regions. 5-HIAA slightly decreased in NCL dialysates. Amphetamine effects were delayed in NCL compared with the striatum. In conclusion, effects of amphetamine on the pigeon's ascending monoamine systems resemble those found in mammals, suggesting similar regulatory properties. The neurochemical differences between NCL and LPO parallel those between associative regions, such as PFC and dorsal striatum in mammals. They may reflect weaker regulation of extracellular DA, favoring DAergic volume transmission, in associative than striatal forebrain regions. J. Comp. Neurol. 446:58–67, 2002. © 2002 Wiley-Liss, Inc.

Indexing terms: associative; sensorimotor; dopamine; amphetamine; aves; microdialysis

In the mammalian brain, dopamine (DA) transmission is critical for sensorimotor functions in the striatum (Schwarting and Huston, 1996) as well as for associative functions, for example, in the prefrontal cortex (PFC) (Sawaguchi and Goldman-Rakic, 1991; Watanabe et al., 1998; Robbins, 2000). These different DA functions appear to be associated with a different DA homeostasis, which depends on the balance of synthesis, degradation, release, and most importantly, synaptic reuptake of DA by the DA transporter (Elsworth and Roth, 1997; Gainetdinov et al., 1998). In the PFC, for example, capacities for reuptake of extracellular DA by the DA transporter are lower, lifetime as well as proportion of released extracellular DA are larger, and released DA can diffuse over much longer distances than in the striatum, where DA reuptake is

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*Correspondence to: Bettina Diekamp, Ruhr-Universität Bochum, AE Biopsychologie, Fakultät für Psychologie, GAFO 05/616, 44780 Bochum, Germany. E-mail: bettina.diekamp@ruhr-uni-bochum.de

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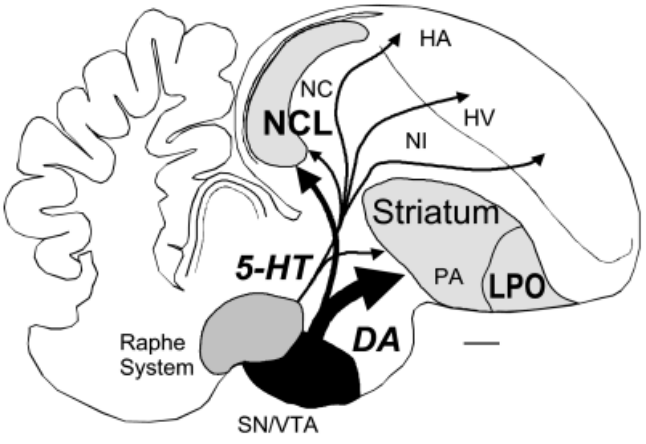

Fig. 1. Parasagittal schematic view of the pigeon brain illustrating the dopaminergic (DA) and serotonergic (5-HT) ascending projections from the brainstem to telencephalic areas. HA, hyperstriatum accessorium; HV, hyperstriatum ventrale; LPO, lobus parolfactorius; NC, neostriatum caudale; NCL, neostriatum caudolaterale; NI, neostriatum intermedium; PA, paleostriatum augmentatum; SN/VTA, substantia nigra/ventral tegmental area. Scale bar = 1 mm.

highly efficient (Sharp et al., 1986; Maisonneuve et al., 1990; Garris and Wightman, 1994; Cass and Gerhardt, 1995; Gainetdinov et al., 1998; Sesack et al., 1998; Pehek, 1999). This finding favors a diffusion-mediated extrasynaptic DAergic volume transmission in the PFC (Zoli et al., 1998), whereas in the striatum, radius and duration of DA function are minutely regulated by a highly active synaptic reuptake system. Thus for DA's role in associative processes on the one hand and its role in sensorimotor control on the other hand, a different regulation of its extracellular concentration may be of fundamental importance.

Aim of the present study was to examine and compare in pigeons the monoamine and in particular DA homeostasis in the neostriatum caudolaterale (NCL) (the term "neostriatum" is a misnomer, because the avian neostriatum is pallial), an associative forebrain structure, and the lobus parolfactorius (LPO), which is part of the avian striatum (Medina and Reiner, 1995) (Fig. 1). Although the avian striatum receives the strongest DAergic midbrain projections in the avian brain, the NCL is also distinguished from the directly surrounding forebrain areas by a dense DAergic innervation from the mesencephalon (Divac and Mogenson, 1985; Waldmann and Güntürkün, 1993; Divac et al., 1994; Wynne and Güntürkün, 1995; Durstewitz et al., 1998, 1999). Although the NCL does not appear to be homologous to the PFC (Striedter et al., 1998; Puelles et al., 1999; Lanuza et al., 2000), behavioral, neuroanatomic, and electrophysiological data characterize it as an associative forebrain structure that may be of comparable significance as the PFC for behavioral control and executive functions, by contributing, for example, to working memory and behavioral flexibility (Mogensen and Divac, 1982, 1993; Güntürkün, 1997; Hartmann and Güntürkün, 1998; Kalt et al., 1999; Kröner and Güntürkün, 1999). DAergic mechanisms were shown to be critical for the complex associative functions of the NCL (Diekamp et al., 2000; Güntürkün and Durstewitz, 2000) as well as for the sensorimotor functions of the avian striatum (Nisticò and Stephenson, 1979; Sanberg and Mark, 1983).

Cognitive and sensorimotor brain areas may be characterized by different DA regulatory mechanisms, such that less rigid regulation of extracellular DA, which is a prerequisite for DAergic volume transmission, is characteristic for associative structures, like mammalian PFC and avian NCL, whereas a firm regulation by synaptic reuptake is prevailing in sensorimotor structures such as the amniote striatum. To test this hypothesis, in vivo microdialysis in connection with high-performance liquid chromatography coupled with electrochemical detection (HPLC-ECD) was used to measure extracellular DA and monoamine metabolites in NCL and LPO of pigeons. Measurements were taken under basal conditions as well as after systemic application of amphetamine (AMPH). AMPH interacts with the regulatory mechanisms of ascending monoamine systems, including the action of monoamine oxidase, vesicular monoamine transporters, and monoamine transporters, especially the DA transporter (Seiden et al., 1993; Jones et al., 1998a). If the ascending monoamine systems of birds and mammals use similar regulatory mechanisms, AMPH's effects on monoamine homeostasis in the avian brain should also be similar to the mammalian brain.

MATERIALS AND METHODS

Animals

Experiments were conducted with 19 adult, unsexed pigeons (*Columba livia*) weighing 360–490 g from local stock. Birds were kept singly in cages and maintained on a normal 12-hour light/dark cycle with water and food available ad libitum. The experiments were performed according to the German guidelines for care and use of animals in neuroscience and were approved by a committee of the State of Nordrhein Westfalen, Germany.

Microdialysis procedure

Microdialysis and HPLC-ECD procedures used in the present study were similar to those previously established in rats (Schwarting and Huston, 1987; Boix et al., 1995). Concentric microdialysis probes were used consisting of a dialysis capillary from regenerated cellulose (ID, 215 μm; OD, 251 μm; molecular mass cut-off 6 kDa; Akzo, Wuppertal, Germany) glued to a 19 mm, 26-gauge stainless steel cannula. The length of the active membrane was 2.5 mm (Fig. 2). A polyethylene tube fixed at the end of the steel cannula served as inlet, a fused silica capillary (ID, 75 μm; Cluzeau, Sainte Foy la Grande, France) inside the probe served as outlet. For collection of dialysates, the polyethylene tube was connected to a microinfusion pump (CMA/100; Semrau, Sprockhövel, Germany). The probes were perfused at 2 μl/min with modified Ringer's solution (147 mM Na^+, 2.3 mM Ca^{2+}, 4 mM K^+, 155.6 mM Cl^-, pH 7; Delta-Pharma, Pfullingen, Germany). Dialysates were collected every 20 minutes (40 μl) into vials containing 10 μl of the internal standard solution (10,000 pg dihydroxybenzylamin in 50 μl 0.05 M perchloric acid) and were immediately stored at −20°C until HPLC-ECD analysis.

For determination of in vitro probe recovery, 2-ml Eppendorf tubes were filled with modified Ringer's solution containing 300 pg of DA and 20,000 pg of dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) per 40 μl. Probes were immersed in this solution, perfused

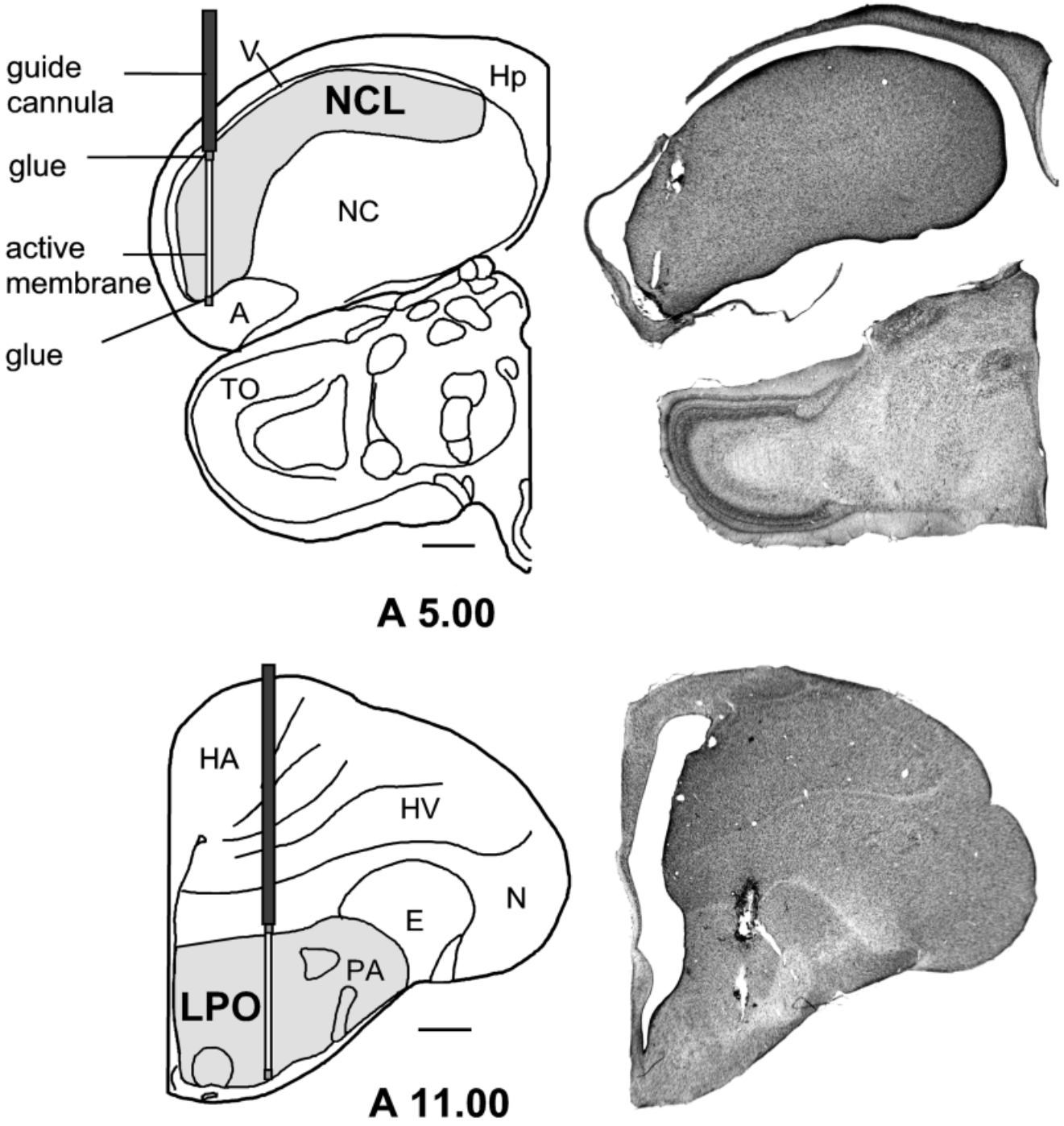

Fig. 2. Schematic frontal views (according to Karten and Hodos, 1967) of the pigeon brain together with corresponding cresyl violet–stained sections illustrating the sampled regions in the pigeon's left NCL (A 5.00) and right LPO (A 11.00). The guide cannulae and inserted microdialysis probes are depicted schematically, and corresponding traces can be discerned in the brain sections. A, archistriatum; E, ectostriatum; HA, hyperstriatum accessorium; HV, hyperstriatum ventrale; Hp, hippocampus; LPO, lobus parolfactorius; N, neostriatum; NC, neostriatum caudale; NCL, neostriatum caudolaterale; PA, paleostriatum augmentatum; TO, tectum opticum; V, ventricle. Scale bars = 1 mm.

at 2 μl/min, and three dialysates were collected with each probe and then analyzed by HPLC-ECD. In vitro recovery rates for DA, DOPAC, HVA, and 5-HIAA were calculated for each probe by dividing the mean dialysate concentrations of DA, DOPAC, HVA, and 5-HIAA by the respective concentrations of the Ringer's solution. Recovery rates

were determined to check for the reliability of probe performance. They were not used to adjust brain dialysate concentrations closer to the true extracellular values, because such an adjustment has been demonstrated to add noise to the measurements and to be rather disadvantageous for the determination of proportions and relative changes of extracellular DA and DOPAC concentrations (Glick et al., 1994).

One to 2 weeks before microdialysis experiments, the pigeons were anesthetized with ketamine (4 mg/100 g; i.m.; Ketavet, Upjohn) and xylazine (0.8 mg/100 g; i.m; Rompun, Bayer) and two guide cannulae (22-gauge stainless steel) were implanted stereotaxically into the left NCL (11-mm guide cannula) and right LPO (16-mm guide cannula) according to the atlas of Karten and Hodos (1967). Cannulae were fixed to the skull with dental cement with their tips aimed above the left NCL (A 5.0, L 7.5, V 1.0) and right LPO (A 11.0, L 2.5, V 5.7), respectively (Fig. 2).

During microdialysis measurements, pigeons were anesthetized with urethane (1.25g/kg; i.m.). Anesthesia has been shown to have no effect on monoamine metabolism and AMPH effects in forebrain regions of anesthetized rats (Sharp et al., 1986; Butcher et al., 1988; Maisonneuve et al., 1990; Moghaddam et al., 1990), yielding essentially the same results as in awake animals (Zetterström et al., 1983; Kuczenski and Segal, 1989; Pehek, 1999) and, therefore, should not interfere with the neurochemical measurements. Pigeons were wrapped into a heat insulation foil to maintain their body temperature at a physiological level of approximately 40°C. Measurements were performed at room temperature at approximately 20°C.

While being already perfused with Ringer's solution, the microdialysis probes were inserted through the guide cannulae into the left NCL and the right LPO. Collection of dialysates started immediately after probe insertion, although samples 1–4 were rejected allowing the brain extracellular space to stabilize after probe insertion. After collection of nine samples, 11 pigeons were injected with D-amphetamine sulfate (2.3 mg/kg; i.m.; equivalent to 1.7 mg of D-AMPH), and 8 pigeons were injected with 0.5 ml of vehicle, i.e. Ringer's solution, as control. D-amphetamine sulfate (Sigma) was administered by injecting the appropriate volume of Ringer's solution containing 2 mg/ml of the drug. After the injection of AMPH or vehicle, another 11 dialysates were collected from LPO and NCL.

After the microdialysis experiment, pigeons were deeply anesthetized with an overdose of equithesin (5.5 ml/kg) and perfused transcardially with saline followed by 4% phosphate buffered formaldehyde (pH 7.4). The brains were removed and cresyl violet–stained 40-μm frontal sections were prepared according to standard histologic protocols. Positions of the dialysis capillaries within the left NCL and right LPO were histologically verified and determined according to the atlas of Karten and Hodos (1967) and the anatomic borders of the NCL as defined by Waldmann and Güntürkün (1993) (Fig. 2). Photographic documentation was carried out with an AxioCam color camera attached to an Olympus BH2 microscope. Digital images were processed with Photoshop 5.5 software (Adobe, Mountain View, CA) and the Fuji "MediaLab" printer device.

HPLC-ECD analysis of dialysates

Dialysates were assayed for DA, DOPAC, HVA, and 5-HIAA by HPLC-ECD. A total of 45 μl of the mixture of 40 μl of dialysate and 10 μl of internal standard solution was injected by a refrigerated (9°C) autoinjector (CMA/200; Semrau, Sprockhövel, Germany) onto a 125-mm-long Nucleosil C-18 reversed phase column filled with 5-μm particles (Macherey & Nagel, Düren, Germany). The mobile phase was pumped through the HPLC-ECD system with a flow rate of 1 ml/min (L-6000 HPLC pump; Merck-Hitachi, Darmstadt, Germany). The composition of the aqueous mobile phase was 0.15 M chloracetic acid, 0.12 M NaOH, 0.67 mM EDTA, 0.86 mM sodium octylsulfate, 3.5%(v/v) acetonitrile, and 1.8%(v/v) tetrahydrofuran, adjusted to pH 3.0. The working potential of the electrochemical flow cell (VT-03; Antec, Leyden, Netherlands) was set at + 0.7 V vs an Ag/AgCl reference electrode. The HPLC-ECD system was calibrated with an external standard (0.05 M perchloric acid containing 30 pg DA and 2,000 pg HVA, DOPAC, and 5-HIAA per 40 μl). Sample concentrations were corrected by using the internal standard. Detection limits, i.e., concentrations yielding a signal corresponding to three times noise level, were approximately 5 pg of DA, 5–15 pg of DOPAC, and 20–150 pg of 5-HIAA per 40 μl of dialysate.

Data analysis

Mean dialysate concentrations of the different substances during intervals 5–9 were taken as basal values. The HVA/DOPAC ratio was calculated by dividing the mean basal value (pg/40 μl) of HVA by that of DOPAC. Regional differences between basal values from NCL and LPO were checked for significance by unpaired two-tailed *t* tests. To compare between regions and substances, dialysate concentrations of monoamine metabolites were calculated as percentage of the respective basal values (% basal value). The effects of AMPH on DA, which was only detectable in LPO dialysates, were examined on the basis of the absolute dialysate concentrations (pg/40 μl). This method allowed consideration also of those cases in which DA could reliably be detected only after, but not before AMPH injection (DA concentration was then treated as 0 pg/40 μl); therefore, calculation of DA values as % basal value was impossible. Effects of the AMPH or vehicle treatment on changes in concentrations of the different substances over time were assessed by using separate one-way repeated-measures analysis of variance and one-tailed Tukey's honest significant difference (HSD) tests for post hoc analysis. The one-tailed test for differences between baseline value and percentage change in the dialysis sample was appropriate as there are specific hypotheses concerning the effects of AMPH on brain extracellular concentrations of monoamines and their metabolites (Raiteri et al., 1975; Homan and Ziance, 1981; Zetterström et al., 1983; Butcher et al., 1988; Kuczenski and Segal, 1989; Seiden et al., 1993; Jones et al., 1998a). The statistical significance was set at $P < 0.05$ for all tests. All results are presented as mean ± SEM.

RESULTS

Microdialysis probes had the following in vitro recovery rates for the different substances (n corresponds to the number of probes tested): DA, 7.3 ± 1.1% (n = 18); HVA, 6.0 ± 0.4% (n = 18); DOPAC, 5.6 ± 0.6% (n = 18); and 5-HIAA, 4.8 ± 1.7 % (n = 16). Not all pigeons had probes correctly placed in both NCL and LPO; therefore, in some

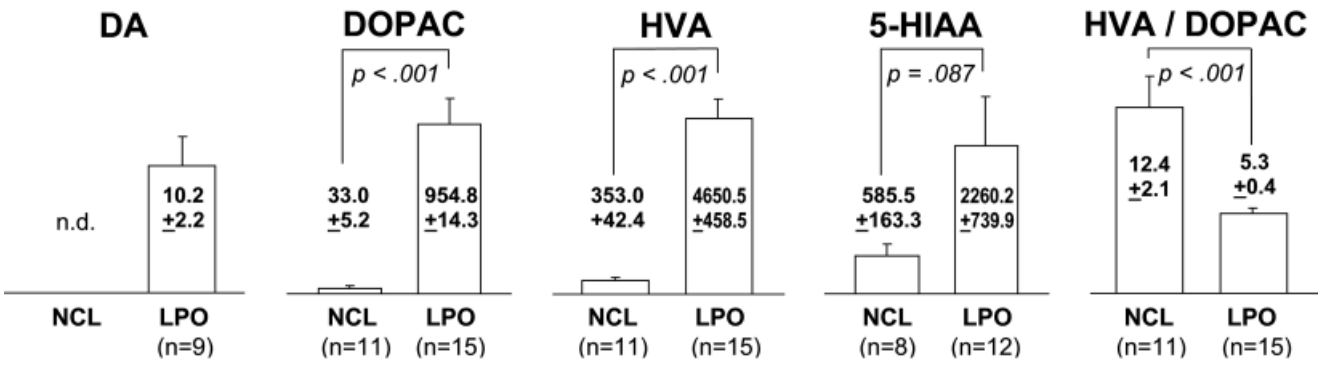

Fig. 3. Basal values ± SEM of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA; pg/40 μl dialysate), and the HVA/DOPAC ratio in dialysates from lobus parolfactorius (LPO) and neostriatum caudolaterale (NCL). Histograms for the different substances are scaled differently. The P values of the t tests for regional differences are indicated. n.d., not detectable.

pigeons, dialysates from only one structure were obtained. NCL dialysates were analyzed from 11 pigeons, 6 of which were injected with AMPH and 5 with vehicle. LPO dialysates were analyzed from 15 pigeons with probes correctly placed in the right LPO, 8 of which were injected with AMPH and 7 with vehicle.

Basal values

Chromatograms obtained from both NCL and LPO dialysates collected under basal conditions (i.e., intervals 5–9) reliably allowed the determination of basal dialysate values of HVA, DOPAC, and 5-HIAA (Fig. 3). The mean basal value of DA in LPO dialysates, determined from nine pigeons, was 10.2 ± 2.2 pg/40 μl. DA in NCL dialysates was usually below the detection limit, i.e., 5 pg/40 μl and, therefore, could not be reliably determined. Basal values of the DA metabolites HVA and DOPAC were significantly higher in dialysates from LPO compared with dialysates from NCL (HVA, $t_{24} = 7.96$, $P < 0.001$; DOPAC, $t_{24} = 5.60$, $P < 0.001$). The basal value of HVA was approximately 13 times that of DOPAC, approximately 30 times higher in LPO than in NCL dialysates. In both the NCL and LPO, HVA was the main DA metabolite (HVA/DOPAC ratio >1). Yet, in dialysates from NCL, the basal HVA/DOPAC ratio was more than two times higher than in dialysates from LPO ($t_{24} = 3.93$, $P < 0.001$). Basal values of the 5-HT metabolite 5-HIAA were also determined and tended to be higher in dialysates from LPO than NCL (Fig. 3). However, this difference was not consistent and did not reach statistical significance ($t_{18} = 1.81$, $P = 0.087$).

Effects of amphetamine on dopamine

After injection of AMPH, concentrations of DA in LPO dialysates were significantly increased compared with basal values ($F_{11,66} = 5.388$, $P < 0.001$), whereas DA concentrations were not affected by vehicle injections ($F_{11,66} = 1.483$, $P = 0.159$) (Fig. 4). On average, DA concentrations in LPO dialysates were approximately six times basal value after the injection of AMPH. Post hoc analysis revealed a stable, significant DA increase above basal levels between 20 and 220 minutes after AMPH administration ($P < 0.003$; Tukey's test). A marked peak concentration of DA after injection of AMPH was not observed. After injection of vehicle, DA levels remained constant over the entire measuring period. DA was not detectable in dialysates from NCL; neither under basal conditions nor after injection of AMPH.

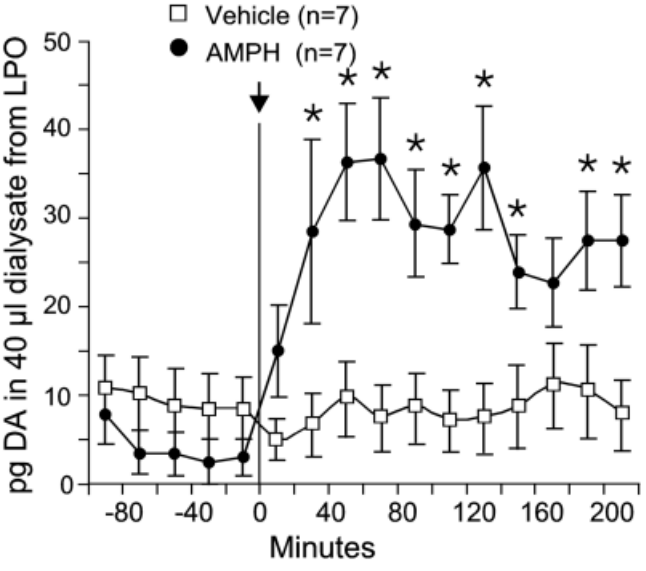

Fig. 4. Effects amphetamine (AMPH) and vehicle injections on dopamine (DA) concentrations (mean±SEM) in lobus parolfactorius (LPO) dialysates. Vehicle or AMPH was administered at time 0 minutes, as indicated by the arrow. Basal values are calculated as mean of the dialysates taken before injection of vehicle or AMPH. Asterisks indicate significantly higher value than basal value ($P < 0.05$, post hoc Tukey's honest significant difference test).

Effects of amphetamine on monoamine metabolites

Injection of AMPH also affected dialysate concentrations of DA metabolites (Fig. 5). Concentrations of DOPAC were significantly reduced after injection of AMPH, both in NCL and LPO compared with basal values ($F_{11,55} = 7.866$, $P < 0.001$ and $F_{11,77} = 33.638$, $P < 0.001$, respectively). A significant decrease after administration of AMPH was also observed for HVA concentrations, both in

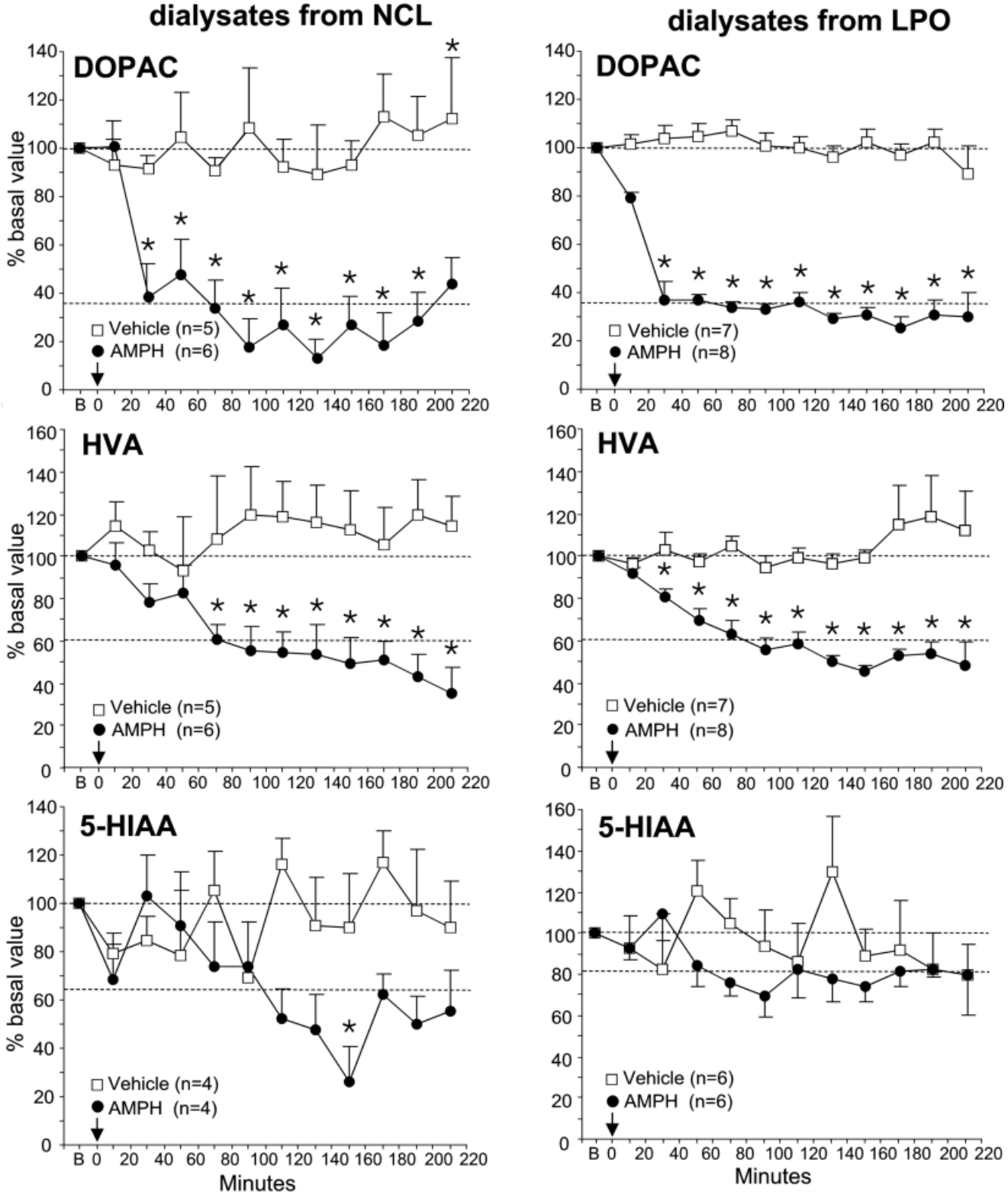

Fig. 5. Effects of amphetamine (AMPH) and vehicle injections on dialysate concentrations (mean±SEM) of monoamine metabolites separated according to substances (dihydroxyphenylacetic acid [DOPAC], homovanillic acid [HVA], and 5-HIAA) and regions (NCL and LPO). Vehicle or AMPH were administered at time 0 minutes. Upper horizontal lines indicate 100% basal value; lower horizontal lines indicate mean concentration after AMPH injection. The overall average of basal values (B) in pg/40 μl dialysate is given in Figure 3. Asterisks indicate significant difference between corresponding samples ($P < 0.05$, post hoc Tukey's honest significant difference test).

NCL and LPO ($F_{11,55} = 6.291$, $P < 0.001$ and $F_{1,12} = 39.040$, $P < 0.001$, respectively). Injection of AMPH also reduced 5-HIAA release in NCL ($F_{11,33} = 3.055$; $P < 0.007$) but not in LPO ($F_{11,55} = 0.982$, $P = 0.473$). Vehicle injections never affected dialysate concentrations of monoamine metabolites ($F < 1.116$, $P > 0.367$).

Post hoc comparisons between baseline values and metabolite concentrations over time revealed substance- and region-dependent differences concerning the effects of AMPH injection. Changes in levels of DOPAC occurred most rapidly, whereas the decrease of HVA concentrations set in later and also reached its full extent later. Additionally, significant changes of DOPAC and HVA concentrations were delayed in NCL compared with LPO dialysates for at least 20–40 minutes (1–2 sampling intervals). In NCL and LPO, levels of DOPAC were reduced on average to approximately 40% basal value. AMPH immediately caused a significant reduction in DOPAC concentrations in LPO ($P < 0.031$, Tukey's test). In NCL, this reduction occurred with a short delay, i.e., the second sample showed significant reduction of DOPAC compared with baseline ($P < 0.004$). Concentrations of DOPAC remained low for all other samples taken over the 220-minute measuring period ($P < 0.001$). Average concentrations of HVA after AMPH injection were only reduced to approximately 60% basal value, in both LPO and NCL dialysates. Also, changes in HVA concentrations were observed later in time than changes in DOPAC concentrations. In LPO dialysates, HVA concentrations were significantly lower than basal values at the second sample after AMPH injection ($P < 0.011$). HVA concentrations decreased for another 40 minutes and then reached a plateau with even significantly lower values than concentrations of samples taken during the initial 80 minutes after AMPH injection ($P < 0.04$). In NCL, significant changes in HVA concentration were observed 40 minutes later than in LPO. The decrease of HVA concentrations in dialysates from NCL continued throughout the entire measuring period.

Effects of AMPH on 5-HIAA concentrations with a reduction to approximately 60% basal value were only observed in NCL, not in LPO. However, 5-HIAA levels fluctuated considerably, and post hoc tests revealed that concentrations in NCL were significantly decreased only approximately 120–140 minutes after injection of AMPH ($P < 0.008$).

DISCUSSION

Data of the present study show a distinct difference in the HVA/DOPAC ratio between NCL, an associative forebrain area, and striatal LPO of pigeons. The high HVA/DOPAC in the NCL, which is also characteristic for mammalian associative structures, reflects the high proportion of extracellular compared with intracellular DA in this region, whereas the lower HVA/DOPAC of the LPO relates to the more effective reuptake in this area. Differences in the regulation of DA between these two regions are supported by the delayed effects of AMPH on the metabolite levels in the NCL compared with LPO. The effects of AMPH on extracellular levels of DA and monoamine metabolites are comparable to those found in different mammalian forebrain regions. In previous microdialysis studies in avian forebrain regions (the associative mediorostral neostriatum/hyperstriatum ventrale and the LPO of chicks), only HVA and 5-HIAA could be reliably monitored, not DA or DOPAC (Gruss and Braun, 1997; Gruss et al., 1999). In addition, the direct neurochemical effects of AMPH on the ascending monoamine systems of the avian brain had not yet been studied. The present study provides data allowing for a comparison of monoamine, especially DA homeostasis in avian associative and striatal forebrain structures and for a comparison with functionally similar, but not always homologous areas of the mammalian forebrain.

Basal values

Although the concentrations of the DA metabolites DOPAC and HVA were markedly higher (30-fold and 13-fold, respectively) in LPO dialysates and DA could only reliably be measured in dialysates from the LPO, no consistent differences in 5-HIAA concentrations were found between LPO and NCL dialysates. This finding fits well with immunohistochemical and biochemical postmortem studies on the monoaminergic innervation of the avian brain. In these studies, a much denser DAergic innervation of the LPO compared with the NCL was found (Juorio and Vogt, 1967; Divac and Mogensen, 1985; Divac et al., 1994; Wynne and Güntürkün, 1995; Metzger et al., 1996; Durstewitz et al., 1999), but a comparable and moderate serotonergic innervation of both telencephalic regions (Challet et al., 1996) was found.

The different ranges of dialysate concentrations of DA (several pg/40 μl) and its metabolites (hundreds to several thousand pg/40 μl) found in the present study are similar to those obtained in comparable microdialysis studies in the forebrain of rats. Concentrations of DA and its metabolites were several times higher in LPO dialysates compared with NCL dialysates, which resembles the proportion between striatal and PFC dialysates (Zetterström et al., 1983; Sharp et al., 1986; Gerhardt and Maloney, 1999). Given that, in rats, DA concentrations are 10 times higher in striatal than in PFC dialysates (Sharp et al., 1986; Pehek, 1999), it is not surprising that in the present study DA concentrations were approximately 10 pg/40 μl in LPO dialysates but virtually below our detection limit of 5 pg/40 μl in NCL dialysates. Considering the different microdialysis procedures, the range of 5-HIAA concentrations obtained in a microdialysis study in the rat forebrain (Adell et al., 1991), showing no significant differences between striatum and PFC, is comparable to that obtained for LPO and NCL dialysates.

The main free metabolite of DA in the extracellular space of the pigeon forebrain is HVA. This finding is in correspondence with previous neurochemical studies in birds (Juorio and Vogt, 1967; Barrett and Hoffmann, 1991; Gruss and Braun, 1997; Gruss et al., 1999; Kostál et al., 1999). Remarkably, the HVA/DOPAC ratio in NCL dialysates was more than twice as high as in LPO dialysates. In dialysates from rat PFC, the HVA/DOPAC ratio is also markedly higher than in dialysates from rat striatum (Sharp et al., 1986; Abercrombie et al., 1989; Maisonneuve et al., 1990; Gainetdinov et al., 1998; Jones et al., 1998b). This difference is thought to reflect a lower reuptake by the DA transporter and, correspondingly, a greater proportion of extracellular DA in associative structures compared with the striatum, because a high proportion of HVA stems from extracellular DA metabolism by catechol-O-methyltransferase, whereas DOPAC is mainly generated from DA within the DAergic terminal by monoamine oxidase (Elsworth and Roth, 1997). Consistently, the activity of the DA transporter as well as its expression is

lower in the PFC compared with the striatum of rats (Garris and Wightman, 1994; Cass and Gerhardt, 1995; Sesack et al., 1998). In dialysates from the mammalian amygdala, also an associative forebrain region, the HVA/DOPAC ratio also appears to be comparatively high, even though very few data are available (Hori et al., 1993).

Effects of AMPH

The magnitude and time course of AMPH-induced changes in DA and monoamine metabolite concentrations in forebrain dialysates observed in pigeons are similar to those reported from mammals. In the striatum of pigeons and mammals, onset and magnitude of DA increase are comparable, although the duration of the AMPH effect is considerably shorter in the mammalian basal ganglia (Zetterström et al., 1983; Butcher et al., 1988; Kuczenski and Segal, 1989; Moghaddam et al., 1990, 1993; Jones et al., 1998a; Pehek, 1999). In pigeons, as in mammals, concentrations of DOPAC and HVA decreased after administration of AMPH and the decrease in DOPAC was more pronounced and set in earlier than that of HVA. As for DA, the AMPH effects on DA metabolites seem to be prolonged in the pigeon forebrain compared with mammals. This finding indicates that, after systemic application, AMPH remains active for a longer time in the avian brain than in the mammalian brain where it seems to be inactivated very rapidly. Moreover, the action of AMPH seems to be delayed in the NCL compared with the LPO, just as in the PFC compared with the mammalian striatum (Moghaddam et al., 1990, 1993; Pehek, 1999). Lower expression of the DA transporter in the PFC is probably responsible for this difference (Sesack et al., 1998). A delayed AMPH effect compared with the striatum has also been indicated for the rat amygdala (Harmer et al., 1997). Further studies applying AMPH directly to the NCL or LPO by reverse microdialysis may be useful to support that different effects of systemic AMPH in NCL and LPO reflect differences in local mechanisms of DA regulation.

The decrease of 5-HIAA dialysate concentrations after AMPH injection was least pronounced and did not even reach statistical significance for LPO dialysates. This finding again is comparable to mammals, where dialysate concentrations of 5-HIAA were found to be markedly less affected by AMPH than DA metabolite concentrations (Zetterström et al., 1983; Butcher et al., 1988; Kuczenski and Segal, 1989). The greater extent of 5-HIAA decrease in NCL compared with LPO dialysates hints at a different regulation of serotonin release in these two structures possibly due to different functional properties of regulatory mechanisms at serotonergic terminals (Raiteri et al., 1975; Homan and Ziance, 1981). Additionally, it is also possible that transmitter release at serotonergic terminals in NCL and LPO is differentially regulated by DAergic pathways on which AMPH exerts its main effects (Kuczenski and Segal, 1989; Mendlin et al., 1999).

The neurochemical similarities between birds and mammals are supported by similar behavioral effects of AMPH (Goodman, 1981; Idemudia and McMillan, 1984). Thus the regulatory mechanisms of ascending monoamine systems, in particular DA systems, seem to be very similar in birds and mammals. These mechanisms include the interplay of monoamine oxidase, vesicular monoamine transporters, the DA transporter, and possibly also the 5-HT transporter (Homan and Ziance, 1981; Seiden et al., 1993; Jones et al., 1998a). In addition, interactions between DAergic and serotonergic pathways may be responsible for an increase of extracellular 5-HT and a concomitant decrease of extracellular 5-HIAA after AMPH injection (Kuczenski and Segal, 1989; Mendlin et al., 1999). Altogether, the neurochemical data provided by the present study corroborate the existence of functionally very similar mesotelencephalic systems in birds and mammals, i.e., two vertebrate classes that phylogenetically separated more than 200 million years ago (Bock, 1967).

Functional significance of different modes of DA regulation in the striatum and associative forebrain in mammals and birds

The avian NCL and the mammalian PFC display a complex patchwork of similarities and differences. Both share a dense DAergic innervation (Wynne and Güntürkün, 1995), a highly comparable connectivity pattern (Kröner and Güntürkün, 1999), similar single unit properties (Kalt et al., 1999), as well as a prominent and D1-dependent (Diekamp et al., 2000, Güntürkün and Durstewitz, 2000) contribution to executive functions (Mogensen and Divac, 1982, 1993; Güntürkün, 1997; Hartmann and Güntürkün, 1998). On the other hand, numerous differences are obvious. The NCL is unlayered (Durstewitz et al., 1999), lacks a thalamic afferent comparable to the mammalian nucleus mediodorsalis (Metzger et al., 1996; Kröner and Güntürkün, 1999, Lanuza et al., 2000), displays baskets as a morphologic feature of DAergic innervation (Wynne and Güntürkün, 1995), and reveals a substantially different pattern of gene-marker expression than mammalian neocortical areas during development (Puelles et al., 1999). If this mosaic of similarities and differences constitutes the result of a convergent evolution, it is conceivable that a comparable evolutionary pressure shaped different constituents of avian and mammalian pallial structures into a similar functional system. Recently, based on developmental studies and comparisons of calcitonin gene-related peptide immunoreactivity in the avian and mammalian forebrain, it has been suggested that the avian associative neostriatum may also be comparable to the basolateral part of the mammalian amygdala (Lanuza et al., 2000). The amygdala—similar to the PFC as well as the NCL—receives tegmental DA projections that appear to be involved in associative processes (Hori et al., 1993; Harmer and Phillips, 1999; Nader and LeDoux, 1999; Fried et al., 2001).

The present study and previous microdialysis experiments in mammals revealed a higher extracellular HVA/DOPAC ratio and a delayed action of AMPH in the associative NCL as well as in associative structures of the mammalian brain, like PFC and amygdala, compared with the striatum (Sharp et al., 1986; Abercrombie et al., 1989; Maisonneuve et al., 1990; Moghaddam et al., 1990, 1993; Hori et al., 1993; Harmer et al., 1997; Pehek, 1999). The differences between mammalian associative and striatal regions likely reflect a less active system of synaptic DA reuptake in the former ones, resulting in a diffusion-mediated volume transmission by DA (Garris and Wightman, 1994; Cass and Gerhardt, 1995; Gainetdinov et al., 1998; Jones et al., 1998b; Sesack et al., 1998). Thus the differences in DA homeostasis between NCL and LPO may also reflect a lower synaptic DA reuptake in the NCL. This mechanism would then suggest that, in the NCL, DA

could diffuse out of the synaptic cleft and activate extrasynaptic DA receptors by means of volume transmission until its actions are terminated by dilution in the extracellular space, whereas in the LPO, DA signaling is spatially and temporally regulated by a more active synaptic reuptake system, limiting DA's actions to the synaptic cleft.

Two further findings support the assumption of extrasynaptic volume transmission in the NCL. First, extrasynaptic D1 receptors have been found in the neostriatum dorsocaudale, a region of the chicken brain corresponding to the pigeon NCL (Schnabel et al., 1997; Braun et al., 1999). Additionally, D1 receptors are the predominant DA receptors in the pigeon NCL (Durstewitz et al., 1998, 1999). Avian D1 receptors seem to be very suitable for DAergic volume transmission as—in addition to the two subtypes found in mammals (Sunahara et al., 1991)—they include an additional third receptor subtype that has very high DA affinity (Demchyshyn et al., 1995) and, thus, is suitable for activation by low extrasynaptic DA concentrations (Zoli et al., 1998).

The DAergic volume transmission in the NCL of pigeons is complemented by the fact, that many DA fibers in the NCL densely coil around the somata and initial dendrites of postsynaptic targets, thus forming "baskets" around neurons expressing the D1-receptor (Wynne and Güntürkün, 1995; Durstewitz et al., 1998, 1999). Due to this morphologic arrangement, a short burst of tegmental DA neurons should produce a massive release of DA, which quickly reaches regionally homogeneous concentrations around somata and initial dendrites of target neurons. Thus basket-type DA fibers and the low DA transporter activity could represent two synergistic features favoring DAergic volume transmission.

In conclusion, the similarities between birds and mammals concerning the different DA homeostasis in associative compared with sensorimotor forebrain regions suggest distinct modes of DA regulation to be of fundamental functional importance. On the one hand, a firm DA regulation by synaptic reuptake might be essential for the control of fast and accurate movements by the sensorimotor striatum. Accordingly, defective reuptake of DA in the striatum has been implicated in motor deficits of aged rats (Gerhard and Maloney, 1999). On the other hand, DAergic volume transmission may represent a mechanism whereby DAergic midbrain input broadcasts errors in the prediction of stimuli's or actions' biological significance as a global reinforcement or teaching signal, guiding selection of appropriate behavioral reponses, to associative forebrain structures (Montague and Sejinowski, 1994; Zoli et al., 1998; Schultz and Dickinson, 2000).

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