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The rotational model and microdialysis: Significance for dopamine signalling, clinical studies, and beyond

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ABSTRACT

The detailed anatomy of the monoamine pathways of the rat by the students of Nils-Åke Hillarp provided the basis for a neurocircuitry targeting pharmacology. Further progress was achieved by the introduction of 6-hydroxydopamine as a tool for performing specific lesions, leading to the first stereotaxic mapping of the monoamine pathways in the rat brain by Urban Ungerstedt at the Karolinska Institutet, Stockholm, Sweden. Unilateral intracerebral injections with 6-hydroxydopamine led to the proposal of 'Rotational Behaviour', as a classical model for screening drugs useful for alleviating Parkinson's disease and other neuropathologies. The direction of the rotational behaviour induced by drugs administrated to lesioned rats reveals their mechanisms of action on dopamine synapses, as demonstrated when rotational behaviour was combined with microdialysis. The model was useful for proposing a role of dopamine receptors in the gating of the flow of information through different efferent pathways of the basal ganglia. It is established now that the coupling of dopamine receptors is regulated by a number of proteins acting as GTPases, the regulators of G-protein signalling (RGS) family. More than 20 RGS proteins have been identified, organised into subfamilies based on structural features and specificity for different G-protein subunits. These protein subfamilies represent alternative pathways gating the flow of information generated in the basal ganglia.

Microdialysis has been developed as a general tool for studying tissue and organ chemistry, leading to a truly translational venture as microdialysis is brought into clinical use, monitoring energy metabolism following global or focal ischemia in the neurosurgery and general medicine scenario.

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Abbreviations: CNS, Central nervous system; COMT, catechol-*o*-methyl transferase; CYP, Cytochrome P450; DA, Dopamine; ED, Electrochemical detector; GABA, γ-Aminobutyric acid; G proteins, Guanine nucleotide binding proteins; GTP, Guanine triphosphate; HPLC, High performance liquid chromatography; 6-OHDA, 6-Hydroxydopamine; 5-HT, 5-Hydroxy-tryptamine; IL, Interleukin; MAO, Monoamine oxidase; NA, Noradrenaline; NOS, Nitric oxide synthase; RGS, Regulators of G-protein signalling; SAH, Subarachnoid haemorrhage; TH, Tyrosine hydroxylase; TNF, Tumour necrosis factor; VTA, Ventral tegmental area.

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1. The beginning

1.1. The Falck and Hillarp formaldehyde fluorescence method is brought to the Karolinska Institutet

The students of Nils-Åke Hillarp at the Karolinska Institutet, Stockholm, Sweden, provided the first detailed information about the intraneuronal localisation of monoamines in the rat brain (Dahlström and Fuxe, 1964, 1965), based on the Falck and Hillarp formaldehyde fluorescence method for catecholamines and related compounds (Falck et al., 1962), which Hillarp had brought with him to Stockholm. The method showed terminal areas as well as cell bodies. Over the following years, using selective neurochemistry, stereotaxic technique, and localised brain lesions, Urban Ungerstedt reported a detailed mapping of neuronal pathways, synthesising, storing and releasing noradrenaline (NA), dopamine (DA) and 5-hydroxy-tryptamine (5-HT), identifying the localisation of their cell bodies, axon trajectories and terminal targets (Ungerstedt, 1971a). The mapping of the monoamine pathways was progressively improved by important technical developments, such as that provided by the glyoxylic acid fluorescence method, allowing description of dopaminergic axons and fibers ascending to innervate the telencephalon (Lindavall and Björklund, 1974).

1.2. Developments, immunocytochemistry, electron microscopy, electrophysiology

Immunocytochemistry, based on the indirect immunofluorescence technique developed by A.H. Coons and collaborators (Coons, 1958), provided a quality breakthrough, leading to the mapping of tyrosine-hydroxylase-immunoreactive neurons in the rat brain (Hökfelt et al., 1984), but also in the brains of other animals including humans (see Parent, 1986). Electron microscopy allowed the morphology of DA innervation to be studied in exquisite detail (Hökfelt and Ungerstedt, 1973). Their close association with spines and excitatory synapses gave rise to the suggestion that DA terminals act specifically on synaptic strength rather than on general membrane properties (Freund et al., 1984). The idea is now supported by physiological studies, demonstrating that the long-term depression that usually follows high frequency stimulation of the corticostriatal system *in vitro* can be reversed to become a long-term facilitation by the pulsatile application of DA (Wickens et al., 1996). Stimulation through electrodes supporting electrical self-stimulation was then shown to result in D_1 receptor dependent long-term potentiation of corticostriatal synapses *in vivo* (Reynolds et al., 2001). These, along with many other *in vitro* studies (e.g. Calabresi et al., 1996; Centonze et al., 2001), have suggested that DA is capable of modifying corticostriatal transmission.

Recent calculations, from *in vivo* anatomical studies, suggest that each of the approximately 10,000 DA cells in the rat brain give rise to 370,000 synapses in the striatum. So whatever they do it seems unlikely that a single DA cell can have much specificity about which synapses it influences—an idea that is supported by many observations suggesting that the system works in a kind of 'volume transmission' mode (Agnati et al., 1986; Arbuthnott and Wickens, 2007).

1.3. Reconstruction of DA neurons: the organotypic culture model

The organotypic culture model developed by B.H. Gähwiler in Zurich, Switzerland, (Gähwiler, 1981) has been useful for describing details of the nigrostriatal dopaminergic circuitries (Plenz and Kitai, 1996a,b), and individual cell reconstructions, as that shown in Fig. 1, where a dopaminergic neuron is depicted, with axons navigating towards their target region, where they branch and appose to local cells (Klawitter et al., 2005). Similar preparations are useful for exploring specific morphological and electrophysiological features of DA neurons working in a physiologically relevant *in vitro* network (Plenz and Kitai, 1998, 1999; Plenz et al.,

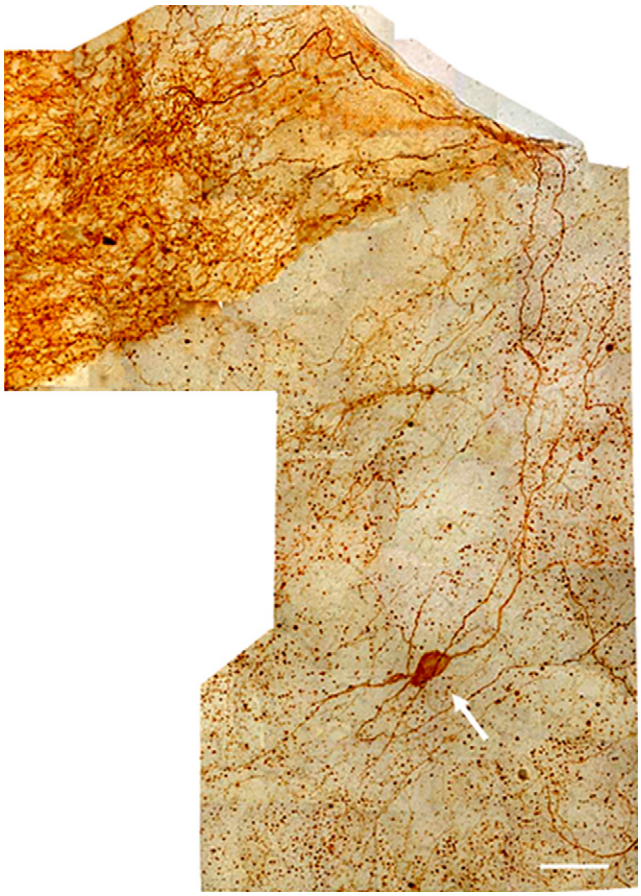

Fig. 1. Tyrosine hydroxylase (TH)-positive neuron in substantia nigra from a triple organotypic culture fixed at DIV 24. A multipolar TH-positive neuron is shown (arrow), with a rich neuritic tree extending to different planes. A possible axon ascends to an intensively TH-positive area where no TH-positive cell bodies are seen, branching and forming a dense network, probably representing a target region (bar: 20 μm). (Modified from Klawitter et al., 2005, with permission.)

1998). Indeed, we have also reported that the major neurocircuitries of the basal ganglia can be reconstructed with organotypic cultures (Gomez-Urquijo et al., 1999), enhancing the differences between nigrostriatal and mesolimbic dopaminergic systems. As shown *in vivo* (Hökfelt et al., 1980), co-localisation of DA and cholecystokinin is observed in a larger proportion in ventral tegmental area (VTA) than in substantia nigra (Gomez-Urquijo et al., 1999). The organotypic culture model has also been useful for magnifying the interactions between tyrosine-hydroxylase- and nitric oxide synthase (NOS)-positive neuronal systems, in mesencephalon and telencephalon, suggesting a reciprocal modulation that has not yet being described *in vivo* (Herrera-Marschitz et al., 2000). The organotypic culture model has also been useful for illustrating selective effects of perinatal asphyxia on neurocircuitries involving DA- and NOS-positive neurons (Klawitter et al., 2007).

2. Experimental and clinical intuitions

In 1959, Arvid Carlsson proposed that DA may be a neurotransmitter in the CNS, involved in the control of motor function and Parkinson's disease, which was confirmed by Hornykiewicz (1966; see 2002), who reported that the lack of DA was a characteristic of the brains of patients suffering of Parkinson's disease, although at that time few neuroanatomists would accept the existence of a DA containing nigrostriatal pathway, until fully mapped by the amino group in Stockholm. The pioneering work was by Nils-Erik Andén (Andén et al., 1966), who studied the features of the ascending pathway using unilateral hemisections. The lesion, performed at the level of the lateral hypothalamus, interrupted the axonal flow of ascending and descending pathways, causing an accumulation of fluorescent material proximal to the lesion, thus making the axons possible to trace in serial sections back towards the substantia nigra (Andén et al., 1964, 1966). The hemisections produced rather extensive damage, including bleeding and necrosis. When recovering from the lesion, the animals showed a postural deviation towards the side of the lesion that could be enhanced and transformed into ipsilateral rotational behaviour whenever the animals were treated with high doses of dopaminergic drugs, such as amphetamine or apomorphine (Andén et al., 1967), reflecting the functional dominance of the intact hemisphere.

3. Neurochemical lesions

3.1. Lesions based on neurotransmitter phenotypes

The concept of a neurochemical lesion, introduced by C.C. Shute and P.R. Lewis (Shute and Lewis, 1966, 1967; Lewis and Shute, 1967) when studying acetylcholine esterase containing pathways in the brain, was dramatically extended following reports describing the use of 6-hydroxydopamine (6-OHDA) for lesioning peripheral NA neurons (Tranzer and Thoenen, 1967, 1968; Malmfors and Sachs, 1968).

3.2. 6-Hydroxydopamine as metabolite of DA

Senoh et al. (1959) discovered and isolated the metabolite 6-OHDA, when studying the enzymatic conversion of DA to noradrenaline in rat tissue homogenates, a reaction catalysed by several oxidases of the cytochrome P450 (CYP) family. Indeed, 6-OHDA can be detected in the urine of rats pre-treated with a monoaminoxidase inhibitor (see Kostrzewa and Jacobowitz, 1974), suggesting a liver metabolism *in vivo*. Brain metabolism has also been suggested, since CYP oxidases have been demonstrated in specific brain regions (Woodland et al., 2008), providing the possibility for *in vivo* formation of 6-OHDA in catecholamine rich areas. No relevant concentrations of 6-OHDA have, however, been reported yet, as to suggest whether this compound reaches relevant concentrations to kill DA neurons, leading to Parkinson's disease.

As shown in Fig. 2, 6-OHDA is 3-hydroxy tyramine with an additional hydroxyl group in the aromatic ring, at the position 6, yielding 3,6-dihydroxy tyramine, probably by oxidases of the CYP family. The formation of hydroxylated compounds by tyrosine hydroxylase has also been proposed, but yielding 2,3-, and/or 3,5

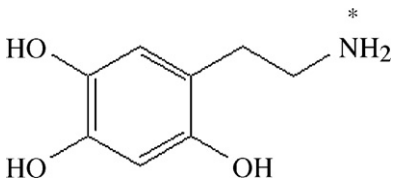

Fig. 2. Chemical structure of 6-hydroxydopamine (6-OHDA). 6-OHDA is a catecholamine with an additional hydroxyl group at the position 2 in the aromatic ring whether following the IUPHAR nomenclature (2,4,5-trihydroxyphenethylamine). Traditionally, however, the number of the hydroxyl groups is referred to the tyramine structure, where a hydroxyl group is in the position 4, whether counted from the alkylamine branch. Thus, dopamine becomes a 3-hydroxy tyramine, while 6-OHDA becomes a 3-6-dihydroxy tyramine. For experimental purposes, 6-OHDA can be conjugated at the amino moiety (*) with an acid, to form a soluble salt, e.g. hydrochloride or hydrobromide, without altering the toxicity of the compound.

compounds, favourable substrates for further oxidation and conjugation, but not for cyclation of the alkylamine branched with the benzene ring.

3.3. Lesions based on neuronal compartmentalisation of neurotransmitters: stereotaxic intracerebral injections

Ungerstedt (1968) showed that by injecting 6-OHDA directly into the brain with a stereotaxic method DA neurons of the ventral mesencephalon could be specifically destroyed (Ungerstedt, 1971b; Hökfelt and Ungerstedt, 1973). α-Methyl-noradrenaline was also injected at different levels of the brain as a retrograde marker, but 6-OHDA was used for disclosing anterograde and retrograde degeneration, identifying the extension of the fluorescent accumulation produced by the treatment. The three monoamines differed in their sensitivity to 6-OHDA. While DA cell bodies in the substantia nigra and DA terminals in the caudate nucleus were very sensitive to the degenerative effect produced by local 6-OHDA administration, 5-HT cell bodies were largely unaffected by local administration of the toxin. As previously shown (Tranzer and Thoenen, 1967, 1968), 6-OHDA could damage NA containing nerve terminals, but not NA cell bodies when intracerebrally administered. The use of a NA uptake inhibitor, e.g. des-methyl-imipramine (DMI) was suggested for preventing any damage on NA terminals (Ungerstedt, 1971b), a practical precaution when lesioning areas receiving extensive NA terminals, which is not the case of the basal ganglia, where the network of NA terminals is diffuse and less intense as compared to that of DA terminals (Ungerstedt, 1971c).

The relevance of 6-OHDA, as a tool for studying the peripheral and CNS was acknowledged by a flood of articles describing various aspects of its pharmacology, leading to a seminal and comprehensive review by Kostrzewa and Jacobowitz (1974), summarising almost 400 articles published up to 1973. In a recent review of the role of 6-OHDA as a model of Parkinson's disease (Simola et al., 2007), the authors concluded that compared to other toxins, 6-OHDA represents an ideal compound for use in the laboratory, providing an easy-to-perform low-cost animal model. Hence, the 6-OHDA model still represents the "gold standard" for investigating novel neuroprotective compounds for DA neurons.

4. Rotational behaviour

4.1. Ipsilateral rotation

When 6-OHDA was injected unilaterally into the rostral part of the DA cell group in the substantia nigra (A9, according to the nomenclature introduced by Dahlström and Fuxe, 1964, 1965), the rats showed a postural deviation towards the side of the lesion, which was transformed into rotational behaviour (ipsilateral rotation), whenever the animal was challenged, e.g. by pinching of its tail (Ungerstedt, 1971b), or by treating the animal with systemic amphetamine (Ungerstedt and Arbuthnott, 1970; Ungerstedt, 1971c). The effect of amphetamine was dose-dependent, and inhibited by various treatments interfering with DA synthesis (e.g. the tyrosine hydroxylase inhibitor, H44/68), or blocking DA receptors (e.g. haloperidol) (Ungerstedt, 1971b), but not by drugs interfering with the vesicular storage of the monoamine (e.g. reserpine), supporting the idea that amphetamine stimulated the release of extragranular, newly synthesised, cytosolic pools of DA (Carlsson et al., 1966).

4.2. Contralateral rotation

In contrast to what was observed by Andén et al. (1967), when lesioning with a knife, the 6-OHDA-lesioned rat rotated towards the opposite side, contralateral rotation, whenever the animal was stimulated with apomorphine (Ungerstedt, 1971b) or any other DA agonist (Fuxe et al., 1974), acting on postsynaptic receptors. The dose of apomorphine required for producing contralateral rotational behaviour was 10-fold lower than that required for producing ipsilateral rotational behaviour in Andén's model. That was an exciting observation, suggesting the occurrence of receptor supersensitivity in the CNS, analogous to that observed in the periphery following a lesion of the ganglion neuron innervating the nictitating membrane (Cannon and Rosenbleuth, 1949; Langer, 1966).

4.3. The direction of rotational behaviour reflects the action of drugs on presynaptic or postsynaptic mechanisms

The direction of the rotational behaviour produced by systemic administration of several drugs to unilaterally 6-OHDA-lesioned rats closely corresponds to their mechanism of action on DA synapses. Ipsilateral rotation is produced by increasing the bioavailability of DA in the synaptic cleft of the intact side, i.e. by stimulating DA release (e.g. amphetamine); inhibiting DA reuptake (e.g. nomifensine); or inhibiting the catabolic enzymes, monoamine oxidase (MAO; e.g. nialamide), or catechol-*O*-methyl transferase (COMT; e.g. tolcapone). In contrast, contralateral rotation is produced by drugs directly stimulating postsynaptic DA receptors, probably rendered supersensitive upon the monoamine de-afferentation (see Herrera-Marschitz, 1986) (Table 1).

4.4. The Rotometer

Significant progress was produced by measuring ipsilateral and contralateral turns with a 'Rotometer' (Ungerstedt and Arbuthnott, 1970), developed for the automatic and continuous recording of rotational behaviour. The Rotometer made possible a detailed analysis of the time-course and behavioural patterns elicited by the drugs, constituting a useful tool for screening dopaminergic drugs (Ungerstedt, 1976). The Rotometer also made it possible to test the hypothesis that rotational behaviour is dependent upon the amount of DA receptor stimulation, and upon the extent of DA denervation produced by the 6-OHDA lesion. The final direct demonstration of DA-release and/or receptor dependency of rotational behaviour required another methodological breakthrough, *in vivo* microdialysis (Ungerstedt and Pycock, 1974; Ungerstedt et al., 1982; see Ungerstedt, 1991).

4.5. Models for estimating DA receptor activation

The DA system has been explored utilizing different techniques, rendering its basic structure and function well studied. Work from W. Schultz laboratory (e.g. Schultz, 1997) has associated DA cell firing with reinforcement; confirming and greatly extending early speculations (Crow and Arbuthnott, 1972). Several behavioural models have been developed for estimating DA receptor activation (Ungerstedt, 1971d; Fuxe et al., 1974; Ungerstedt et al., 1975; Ljunberg and Ungerstedt, 1976; Schallert et al., 1978; Tillerson et al., 2001) as a way to hunt for DA replacing drugs and thus search for a cure for Parkinson's disease and parkinsonism.

5. Monitoring neurotransmission release

5.1. In vivo microdialysis

The usefulness of microdialysis as a tool for studying neurotransmitter release in the central nervous system (CNS) or for assaying the metabolism of any other organ is well documented and accepted, and the application scope has been summarised in many excellent reviews. At the time when preparing the present

Table 1
Direction of the rotational behaviour produced by systemic administration of drugs stimulating DA transmission in 6-OHDA-lesioned rats.

Drugs	Ipsilateral	Contralateral
Stimulation DA receptor		
DA (loaded with L-DOPA)	No	Yes
Apomorphine	No	Yes
N-Propylnorapomorphine	No	Yes
SKF 38393	No	Yes
SKF 81297	No	Yes
CY 208-243	No	Yes
CQ 32-084	No	Yes
Piribidil	No	Yes
Bromocriptine	No	Yes
Pergolide	No	Yes
Quinpirole	No	Yes
CU 32-085	No	Yes
Lisuride	No	Yes
Lergotrile	No	Yes
±3PPP	No	Yes
+3PPP	No	Yes
−3PPP	No	Yes
3-phenylPP	No	Yes
BHT 920	No	Yes
OSU6162	No	Yes
Stimulation of DA release		
±Amphetamine	Yes	No
D-Amphetamine	Yes	No
Methamphetamine	Yes	No
p-Methoxyamphetamine	Yes	No
p-Methoxymethamphetamine	Yes	No
Methylenedioxiamphetamine	Yes	No
Stimulation of DA release/stimulation of DA receptors		
1-Amino-3,5-dimethyl-adantamine (D145)	Yes	Yes
Reuptake blockade		
Benztropine	Yes	No
Nomifensine	Yes	No
Lu 19-005	Yes	No
Lu 17-133	Yes	No
Lu 2-098 (compound 8)	Yes	No
MAO inhibition		
Nialamide	Yes	No
Pargyline	Yes	No
Deprenil	Yes	No
COMT inhibition		
Tolcapone	Yes	No

The direction of the rotational behaviour induced by systemic administration of dopaminergic drugs discloses their mechanisms of action on dopamine transmission. L-DOPA (2–50 mg/kg, i.p.; Apoteksbolaget, Sweden); apomorphine (0.005–5 mg/kg, s.c. Apoteksbolaget, Sweden); *N*-propylnorapomorphine (0.1–5 mg/kg, s.c.; Scheering, USA); SKF 38393 (2–20 mg/kg, s.c.; Smith, Kline & French, USA); SKF 81297 (0.5–1.0 mg/kg, s.c.; Smith, Kline & French, USA); CY 208-243 (0.1–0.5 mg/kg, s.c.; Novartis Pharma, Switzerland); CQ 32-084 (0.05–10 mg/kg, s.c.; Sandoz, Switzerland); piribidil (1–50 mg/kg, s.c.; Laboratories Servier, France); bromocriptine (0.2–10 mg/kg, s.c.; Sandoz, Switzerland); pergolide (0.001–0.5 mg/kg, s.c.; Lilly, USA); quinpirole (0.5–1 mg/kg, s.c.; Sandoz, Switzerland); lisuride (0.1–5 mg/kg, s.c.; Scheering, USA); lergotrile (0.5–5 mg/kg, s.c.; Sandoz, Switzerland); ±3PPP (0.5–20 mg/kg, s.c.; Lundbeck, Denmark); +3PPP (1–10 mg/kg, s.c.; Lundbeck, Denmark); −3PPP (5–10 mg/kg, s.c.; Lundbeck, Denmark); 3-phenylPP (5–10 mg/kg, s.c.; Lundbeck, Denmark); BHT 920 (0.05–1 mg/kg, s.c.; Boehringer, Ingelheim/Rhein, Germany). ±amphetamine (0.5–10 mg/kg, s.c.; Sigma, USA); D-amphetamine (0.5–10 mg/kg, s.c.; Sigma, USA); Methamphetamine (2–10 mg/kg, s.c.; Sigma, USA); *p*-Methoxyamphetamine (2–10 mg/kg, s.c.; Romero et al., 2006); *p*-Methoxymethamphetamine (2–10 mg/kg, s.c.; Romero et al., 2006); Methylenedioxyamphetamine (2–10 mg/kg, s.c.; Romero et al., 2006); benztropine (10–20 mg/kg, s.c.; Hoechst, Germany); nomifensine (5–20 mg/kg, s.c.; Hoechst, Germany); Lu 19-005 (5–40 mg/kg, s.c.; Lundbeck, Denmark); Lu 17-133 (10–40 mg/kg, s.c.; Lundbeck, Denmark); Lu 12-098 (compound 8) (10–40 mg/kg, s.c.; Lundbeck, Denmark); nialamide (50–100 mg/kg, s.c.; Pfizer, Germany); pargyline (50–1000 mg/kg, s.c.; Sigma, USA); D145 95–30 mg/kg, s.c.; Merck, USA) (from Herrera-Marschitz, 1986; see Herrera-Marschitz et al., 2007).

article there were 636 reviews on microdialysis in PubMed. In a recent review, Sharp and Zetterström (2007) provide a personal historical account about the beginning of microdialysis and its emergence as a key neuroscience method.

5.2. Dialysing the brain with an artificial blood vessel

There has been some discussion about the origin of the concept of microdialysis, in particular whether Urban Ungerstedt was inspired by the pioneering work of J.M.R. Delgado and co-workers on dialytrodes (Delgado et al., 1972). In fact, both authors worked with different assumptions and goals, and their work was performed in parallel through different developmental routes. Ungerstedt thought about an artificial blood vessel inserted into the parenchyma of deep brain nuclei. When inspecting the histofluorescence of sections of rat brains treated unilaterally with 6-OHDA, Ungerstedt was particularly attracted by the strategic location of blood vessels in catecholamine rich fluorescent regions. The idea of sampling from the extracellular space (Ungerstedt and Pycock, 1974) was partly inspired by the push–pull technique (Gaddum, 1961), developed by J. Glowinski at the INSERM, France (Glowinski, 1974) for characterising the neuropharmacology of the neurocircuitries of the basal ganglia of the cat.

5.3. Analytic chemistry of dialysates

A main issue was the setup for analysing low concentrations of DA, which was possible by technical advances in high performance liquid chromatography (HPLC), coupled to a electrochemical detector (ED), as proposed by the pioneering work of R.N. Adams at the University of Kansas, KA, USA (Adams, 1978; Jonsson et al., 1980).

During the first experiments, only DA could be assayed, digging into low quality and low signal-to-noise ratio chromatographs. A main concern by the reviewers at that time was why we analysed DA, but not the metabolites (Ungerstedt et al., 1982), assuming that, because of their higher concentration, the metabolites would play a more relevant physiological role. A successful collaboration with C.A. Marsden, Nottingham, UK, was required for simultaneously measuring DA and its metabolites (Zetterström et al., 1983), confirming the established knowledge that DA is the physiologically relevant signal (see Zetterström, 1986).

5.4. Selective lesions, rotational behaviour and in vivo microdialysis

An important series of experiments was performed with unilaterally 6-OHDA-lesioned animals, demonstrating that, when a microdialysis probe was inserted into the non-de-afferented neostriatum, DA levels were detected and increased by amphetamine (0.5–5 mg/kg, s.c.), as previously proposed by Fuxe and Ungerstedt (1970). The increase of DA release stimulated by amphetamine correlated with the ability of the drug to elicit ipsilateral rotational behaviour. The peak, as well as the duration of the rotational behaviour, coincided with that of DA release (Ungerstedt et al., 1982; Zetterström et al., 1986). No DA could be detected in the lesioned neostriatum. Nevertheless, following L-DOPA (20 mg/kg, s.c.), the same rats rotated contralaterally, during the time when DA could be detected in a previously silent neostriatum (Zetterström et al., 1986). Interestingly, while a substantial amount of DA could be detected after L-DOPA, that amount was always below basal levels detected in the intact neostriatum, but enough for producing contralateral rotation, lasting for approximately 2 h. That was the first direct demonstration of L-DOPA being decarboxylated in brain regions with a full DA de-afferentation, producing, however, a significant amount of extracellular DA levels to stimulate receptors rendered supersensitive, and to overcome the motor deficit, very much mimicking the principles of volume transmission proposed by Kjell Fuxe and co-workers (Agnati et al., 1986). If DA levels were detected in the lesioned neostriatum, they correlated with the rotational behaviour elicited by DA agonists: the higher the extracellular DA levels

in the lesioned neostriatum, the lower the contralateral rotational behaviour induced by DA agonists (Herrera-Marschitz et al., 1990a,b). That negative correlation was also demonstrated for DA tissue levels (Herrera-Marschitz, 1986; see Herrera-Marschitz et al., 2007).

5.5. Monoamines, amino acids and neuropeptides: testing for neuronal origin

Analytic progress led to simultaneous determination of several endogenous substances in the dialysates. Thus, monoamines, acetylcholine, amino acids, neuropeptides and metabolism products could be measured in the same dialysates, using various HPLC systems, coupled to electrochemical (e.g. monoamines; acetylcholine; γ-aminobutyric acid, GABA); fluorometric (e.g. glutamate, aspartate); UV (e.g. pyruvate, lactate, adenosine) detection systems, or radioimmunoassays (RIA) using specific antisera (e.g. substance P, cholecystokinin, dynorphin). The perfusion media had to be characterised, as well as perfusion variables such as perfusion flow (1–2 μl), sampling period (10–40 min), and volume of the collected dialysate (20–80 μl), to be split through different biochemical assays. Substances in the dialysates were then simultaneously measured under basal and pharmacologically stimulated conditions. Several criteria had to be defined for assessing when changes in the estimated levels reflected neuronal release or passive tissue leakage. Based on physiological studies, the following criteria were considered critical for assessing a neuronal dependence: (i) Dependence upon neuronal firing, examined by inducing K^+-depolarisation, increasing KCl concentration in the perfusion medium (from 2.7 to 50 or 100 mM KCl), or blocking voltage-dependent Na^+ channels by perfusion with toxins like tetrodotoxin (0.1–10 μM). (ii) Exocytotic-Ca^{2+}-dependent-vesicular release, examined by perfusing with Ca^{2+}-free medium, preferably including a chelator (e.g. 2 mM EGTA), or blocking presynaptic vesicles with reserpine. (iii) Dependence upon the integrity of the studied neuronal pathway (see Herrera-Marschitz et al., 1997).

All these criteria have been applied to study several putative neurotransmitters, including DA (Zetterström, 1986; Westerink et al., 1988; Hurd and Ungerstedt, 1989), acetylcholine (Westerink et al., 1988; Herrera-Marschitz et al., 1992a,b), GABA (Osborne et al., 1990), glutamate (Westerink et al., 1988; Herrera-Marschitz et al., 1996), and neuropeptides, such as neurokinin A and substance P (Lindefors et al., 1987), cholecystokinin (You et al., 1994a), and dynorphin (You et al., 1994b).

Dependence upon the integrity of the neuronal pathway implies that extracellular levels have to decrease whenever the identified pathway is selectively damaged, as largely demonstrated for extracellular DA, when measured in 6-OHDA-lesioned animals (Zetterström et al., 1986; Herrera-Marschitz et al., 1990a,b), or following unilateral transection at the mesodiencephalic junction in rats (Janson et al., 1992). A 6-OHDA lesion induced a selective decrease in DA and metabolite levels, but not in 5-HT or its metabolite, 5-hydroxy-indoleactetic acid (5-HIIA), when simultaneously monitored in the lesioned neostriatum (Romero et al., 2006). Conversely, the striatonigral GABA/dynorphin projection was demonstrated by ibotenic acid lesions in the ipsilateral neostriatum, the location of cell bodies of neurons projecting to the substantia nigra reticulata. The lesion resulted in a decrease of GABA and dynorphin, but not in DA release (Herrera-Marschitz et al., 1986; You et al., 1994b). The cholinergic projection from the nucleus basalis magnocellularis to the neocortex was characterised by lesioning the cell body region with ibotenic acid, and then implanting a microdialysis probe into the ipsilateral and/or contralateral neocortex. It was found that the ibotenic acid lesion decreased acetylcholine levels in the ipsilateral neocortex by approximately 70%, demonstrating for the first time the dependence of acetylcholine release upon the integrity of a cholinergic neurocircuitry (Herrera-Marschitz et al., 1990a,b). A cholecystokinin corticostriatal pathway was characterised by combining ipsilateral ibotenic acid neocortical lesions followed by callosotomy, demonstrating that cholecystokinin, but also glutamate, is released from crossed corticostriatal pathways (Herrera-Marschitz et al., 1992a,b; Morino et al., 1992; You et al., 1994a). Interestingly, while the neocortical/callosum lesion decreased striatal glutamate levels, no effect was observed on simultaneously monitored aspartate levels (Herrera-Marschitz et al., 1996).

5.6. Exocytotic versus non-exocytotic release

The development of microdialysis allowed the investigation *in vivo* of important pharmacological paradigms, such as that related to different, exocytotic or non-exocytotic, newly synthesised, releasable pools of DA (Fairbrother et al., 1990a,b). The dependence of the effect of amphetamine upon newly synthesised DA pools was investigated by inhibiting catecholamine synthesis with α-methyl-*p*-tyrosine or by depleting vesicular stores of DA with reserpine. Synthesis inhibition with α-methyl-*p*-tyrosine, but not vesicular depletion with reserpine, inhibited the release of DA induced by amphetamine, demonstrating that newly synthesised cytosolic pools of DA are the targets for behaviourally relevant doses of amphetamine (Butcher et al., 1988).

6. Assessing dopamine receptors by monitoring rotational behaviour

6.1. One-peak, two-peak rotational patterns

Hints about the involvement of different types of DA receptors were obtained when the rotational patterns induced by agonists with various affinities on D_1 or D_2 receptors were analysed. It was found that apomorphine, a D_1/D_2 agonist (Ernst, 1967; Andén et al., 1967; Hyttel, 1986), produced a peculiar two-peak pattern of rotational behaviour, with a first peak of rotation minutes after the administration of the drug, and a second peak at the end of the effect, independently of the dose (Herrera-Marschitz and Ungerstedt, 1984a). That pattern was observed in rats with larger than 95% of DA depletion (Herrera-Marschitz, 1986; see Herrera-Marschitz et al., 2007), and could also be observed following intracerebral administration of apomorphine (Herrera-Marschitz et al., 1985a). A similar pattern could be produced by L-DOPA (Zetterström et al., 1986), and selective D_1 agonists, such as SKF 38393, CY 208243 and SKF 81297 (Herrera-Marschitz et al., 2007). In contrast, DA agonists with a pronounced selectivity for D_2 receptors, such as bromocriptine, pergolide, and quinpirole, produced a rather uniform (single-peaked) pattern of rotational behaviour (see Fig. 3).

6.2. Multiple DA receptors

When these results were first presented (Ungerstedt and Herrera-Marschitz, 1981; Herrera-Marschitz and Ungerstedt, 1984a), there was a general concern about how specific different agonists were on D_1 and D_2 receptor sites. We argued at that time that stimulation of D_2 receptors could be a common mechanism by which all DA agonists produced rotational behaviour, even supposedly selective agonists on D_1, such as SKF 38393, or SKF 81297, which have a residual displacing activity of ^{3}H-spiperone binding (Hyttel, 1986).

6.3. D1, D2 antagonists: competition studies

The demonstration of a selective action on different DA receptors came from competition studies, blocking the rotational

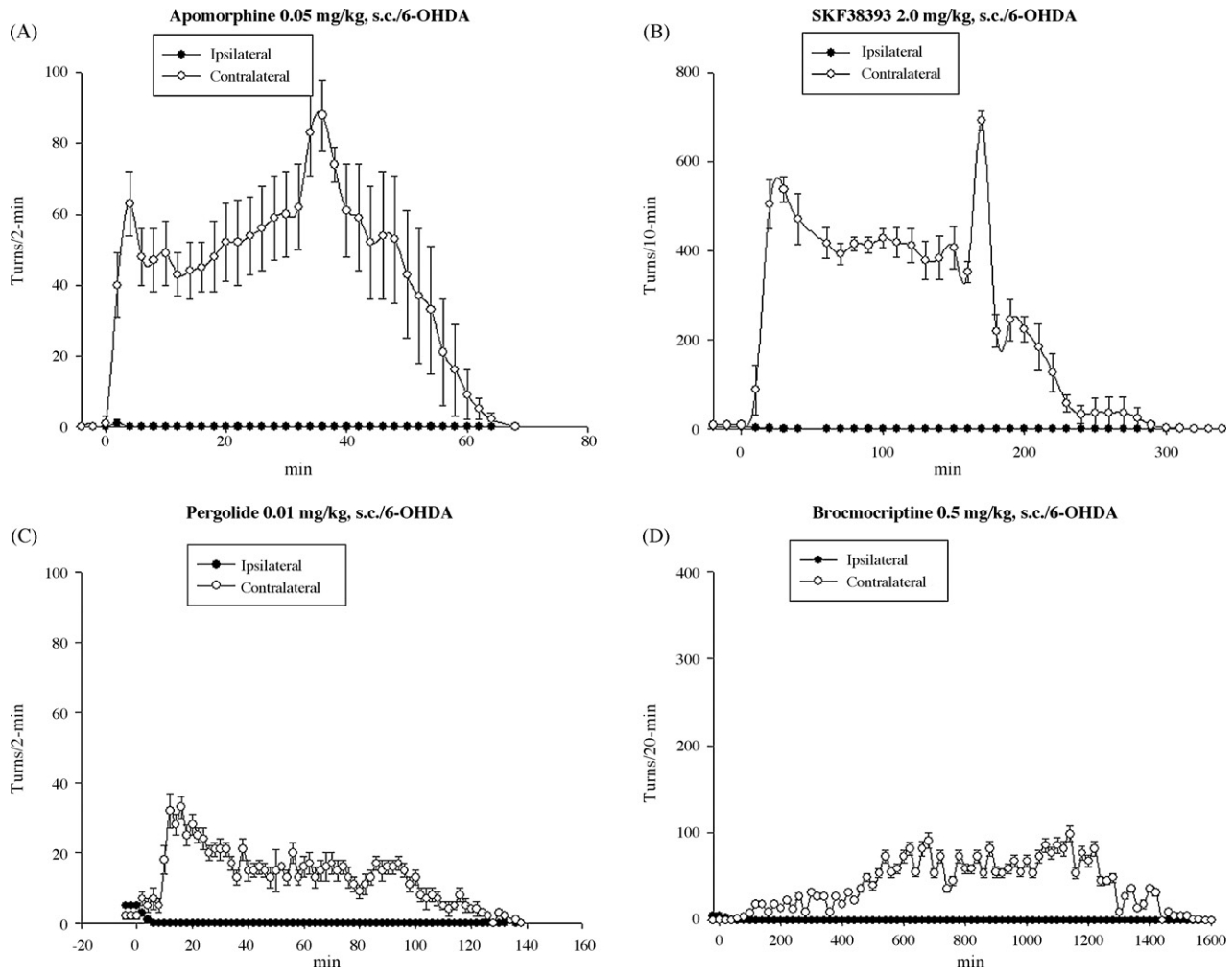

Fig. 3. (A–D) Pattern of contralateral rotational behaviour induced by: (A) apomorphine (0.05 mg/kg, s.c.; $n = 8$); (B) SKF 38393 (2 mg/kg, s.c.; $n = 5$), (C) Pergolide (0.01 mg/kg, s.c.; $n = 8$) and (D) Bromocriptine (0.5 mg/kg, s.c.; $n = 8$) in 6-hydroxydopamine (6-OHDA)-lesioned rats. Vertical lines show S.E.M. Abscissa: min after the respective treatment. Ordinate: turns/min (from Herrera-Marschitz, 1986).

behaviour elicited by D_1, or D_2 preferred agonists. It was found that sulpiride, a selective D_2 antagonist (Trabucchi et al., 1975) inhibited the rotational behaviour elicited by pergolide at doses 1000-fold lower than those required to inhibit an equipotent dose of apomorphine. In contrast, a selective D_1 antagonist, SCH 23390 (Iorio et al., 1983; Hyttel, 1983), was found to be 100-fold more potent to inhibit apomorphine- than pergolide-elicited rotational behaviour. Interestingly, SCH 23390 never fully blocked the rotational behaviour elicited by a low dose of apomorphine (0.05 mg/kg, s.c.), but the pattern was transformed into a single-peaked-pattern of rotation, similar to that elicited by D_2 agonists (Herrera-Marschitz et al., 1984; Herrera-Marschitz and Ungerstedt, 1985) (see Fig. 4).

7. Multiple dopamine receptors gating the striatal outputs

7.1. Striatopallidal versus striatonigral outputs

The neostriatum of rodents, but also the caudate-putamen of higher mammals including humans, projects to the globus pallidus and substantia nigra, largely by non-overlapping pathways: (i) the striatopallidal system, via D_2 receptors on neurons containing GABA and enkephalin; (ii) the striatonigral system, via D_1 receptors on neurons containing GABA, dynorphin and substance P (Christensson-Nylander et al., 1986; see Gerfen and Wilson, 1996). In the striatopallidal pathway, DA binding to D_2 receptors leads to a transduction cascade resulting in a decrease of GABA release (Ferré et al., 1993), and probably enkephalin as well (Cuello and Paxinos, 1978), into the globus pallidus, dis-inhibiting a GABAergic projection to the subthalamus. On the contrary, DA binding to D_1 receptors leads to increased GABA-, substance P- and dynorphin-release into the substantia nigra, pars reticulata (Reid et al., 1988; You et al., 1994c). This is a simplification, but it has been a useful framework for many experimental and clinical observations.

In the substantia nigra, GABA- and dynorphin-terminals provide a negative feedback on DA release, as originally proposed by Andén and Stock (1973), but substance P terminals provide a tonically positive feedback on DA neurons (Reid et al., 1988; see Reid, 1990). Furthermore, DA receptors are also regionally segregated in the substantia nigra, with D_1 receptors located on projecting GABAergic neurons (Savasta et al., 1986; Filloux et al., 1987a; see Robertson, 1992; Bentivoglio and Morelli, 2005), and D_2 receptors on both perikarya and dendrites of DA neurons (Filloux et al., 1987b; Levey et al., 1993; see Robertson, 1992; Bentivoglio and Morelli, 2005).

7.2. Lesioning the striatonigral output

We explored the functional relevance of striatal efferents for rotational behaviour by combining lesions with several neurotoxins, and DA agonists and antagonists. The relevance of the

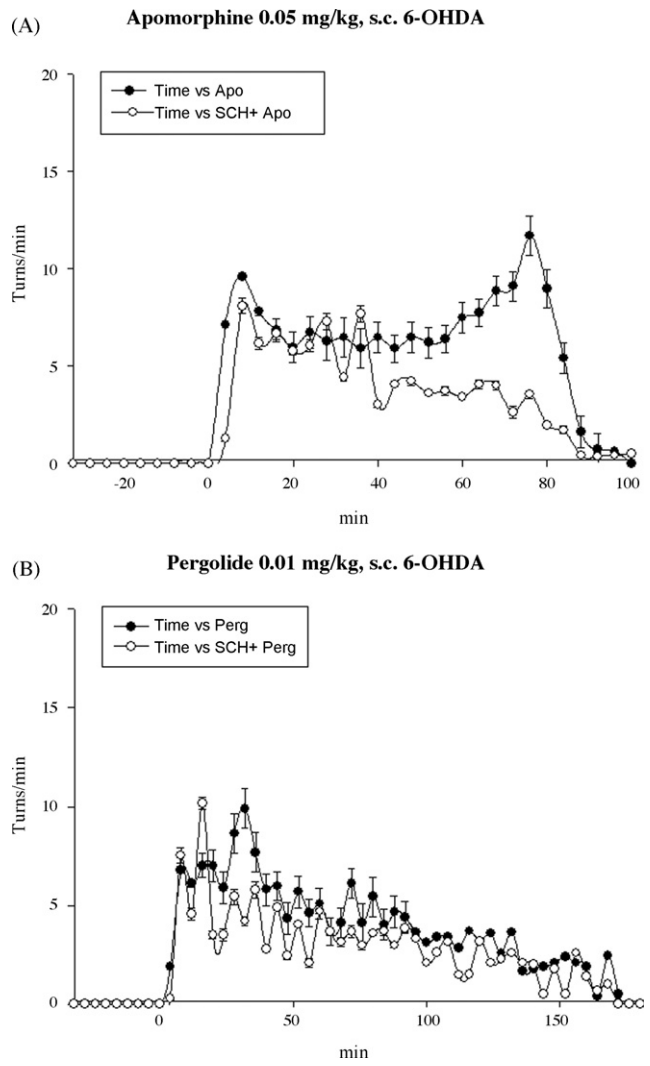

Fig. 4. (A and B) Effect of SCH 23390 (0.05 mg/kg, s.c.; right flank) administered 30 min before apomorphine (0.05 mg/kg, s.c.) (A) or pergolide (0.01 mg/kg, s.c.) (B) (left flank)-induced contralateral rotation. Open circles, the agonist alone; fill circles, SCH 23390 + agonist. Vertical lines show S.E.M. $^{*}p < 0.05$ ($n = 5$ for each experimental group). Abscissa: min after the respective agonist. Ordinate: turns/min (from Herrera-Marschitz, 1986).

striatonigral projection for rotational behaviour elicited by apomorphine in 6-OHDA-lesioned animals was well demonstrated by the almost simultaneous work of Marshall and Ungerstedt (1977), Garcia-Munoz et al. (1977), and DiChiara et al. (1977). An additional lesion to a 6-OHDA-treated animal interrupted the substantia nigra output producing inhibition of the contralateral rotation induced by apomorphine, or converted it to ipsilateral rotation, whenever high levels of apomorphine stimulated normosensitive DA receptors on the intact side.

However, that observation applied to only apomorphine-, but not to pergolide-induced rotational behaviour (Herrera-Marschitz and Ungerstedt, 1984b). Indeed, the pergolide-response was never converted to ipsilateral rotation, even when pergolide was given in such a high dose that the rotational behaviour lasted for more than 42 h. It was argued that pergolide was not able to stimulate normosensitive DA receptors, but pergolide was found to be 10-fold more potent for eliciting ipsilateral rotation in animals with a striatal lesion induced by kainic acid (Herrera-Marschitz and Ungerstedt, 1984a,b), a model for examining normosensitive DA receptors (Schwarcz et al., 1979a).

7.3. Blocking the striatonigral, but not the striatopallidal output

Instead of using kainic acid, we preferred to use ibotenic acid, an analogue inducing a more selective lesion on local cell bodies, sparing 'en passage' fibers, and with low diffusion rate (Schwarcz et al., 1979b). Thus, in a series of animals, ibotenic acid was injected into the caudal region of the substantia nigra reticulata, lesioning local GABAergic, but not DAergic neurons (Herrera-Marschitz et al., 1985b; Christensson-Nylander et al., 1986). After this lesion, apomorphine (0.5–5.0 mg/kg, s.c.) elicited dose-dependent ipsilateral rotation, but, in the same animals, pergolide (0.2–0.5 mg/kg, s.c.) elicited contralateral rotation (cf. Fig. 5C versus D) (see Herrera-Marschitz et al., 2007). Ibotenic acid induced a minor impairment of tyrosine hydroxylase positive neurons, perhaps producing DA de-afferentation of the ipsilateral neostriatum and DA receptor supersensitivity (see arrow in Fig. 5B). Supersensitive DA receptors mediated, probably, the contralateral rotation produced by high doses of pergolide, via activation of the D_2 striatopallidal pathway. Because the ibotenic lesion fully impaired the nigral output, apomorphine could act on only the D_1 striatonigral pathway of the intact side, producing ipsilateral rotation. The effect of apomorphine was antagonised in a dose-dependent manner by low doses of the selective D_1 antagonist SCH 23390 (0.5–500 μg/kg, s.c.), but it was unaffected by the selective D_2 antagonist sulpiride (10-200 mg/kg, s.c.). In contrast, a low dose of sulpiride (10 mg/kg, s.c.) was enough for blocking the effect of pergolide, but not that of apomorphine, even when sulpiride was increased to 200 mg/kg, s.c.) (see Herrera-Marschitz, 1986; Herrera-Marschitz et al., 2007). Thus, these experiments confirmed the D_1 or D_2 dependence of the rotational behaviour induced by apomorphine or pergolide, respectively. The experiments further demonstrated that the effect of apomorphine was conveyed through the substantia nigra pars reticulata, while the effect of pergolide was conveyed through the globus pallidus.

7.4. Basal ganglia efferent pathways

These results provided evidence suggesting that apomorphine ($D_1 > D_2$) and pergolide ($D_2 > D_1$) produced rotational behaviour involving different receptors, linked to different neuronal pathways. Apomorphine produced rotational behaviour by stimulation of the striatonigral pathway, further involving nigrothalamic (DiChiara et al., 1979; Kilpatrick et al., 1980) and nigrotectal (Hopkins and Niessen, 1976; Vincent et al., 1978; DiChiara et al., 1979; Kilpatrick et al., 1982; Chevalier et al., 1981) pathways. Pergolide produced rotational behaviour by stimulating the striatopallidal pathway, projecting to the subthalamus (Rouzaire-Dubois et al., 1980; Van Der Kooy et al., 1981; Kita et al., 1983; Campbell et al., 1985; Haber et al., 1985; Loopuijt and Van Der Kooy, 1985; see Gerfen and Wilson, 1996), or directly to the thalamus (Haber et al., 1985). Another pathway for pergolide effect is the ventral striatum and accumbens projection to the subpallidal region, including the lateral preoptic area and substantia innominata (Jones and Mogenson, 1980; Mogenson and Nielsen, 1983; see Kretschmer et al., 2000).

7.5. Cloning DA receptors

Several of the above discussed experiments were performed long before DA D_1 (Dearry et al., 1990; Monsma et al., 1990; Zhou et al., 1990) and D_2 (Bunzow et al., 1988) receptors were cloned. Indeed, some of the original results were published at a time when Phillip Seeman in Toronto, Canada (Seeman, 1981), reported that the potency of various DA agonists for eliciting rotational behaviour, producing emesis, eliciting stereotypy and alleviating Parkinson's disease correlated with only their IC_{50} values for D_2

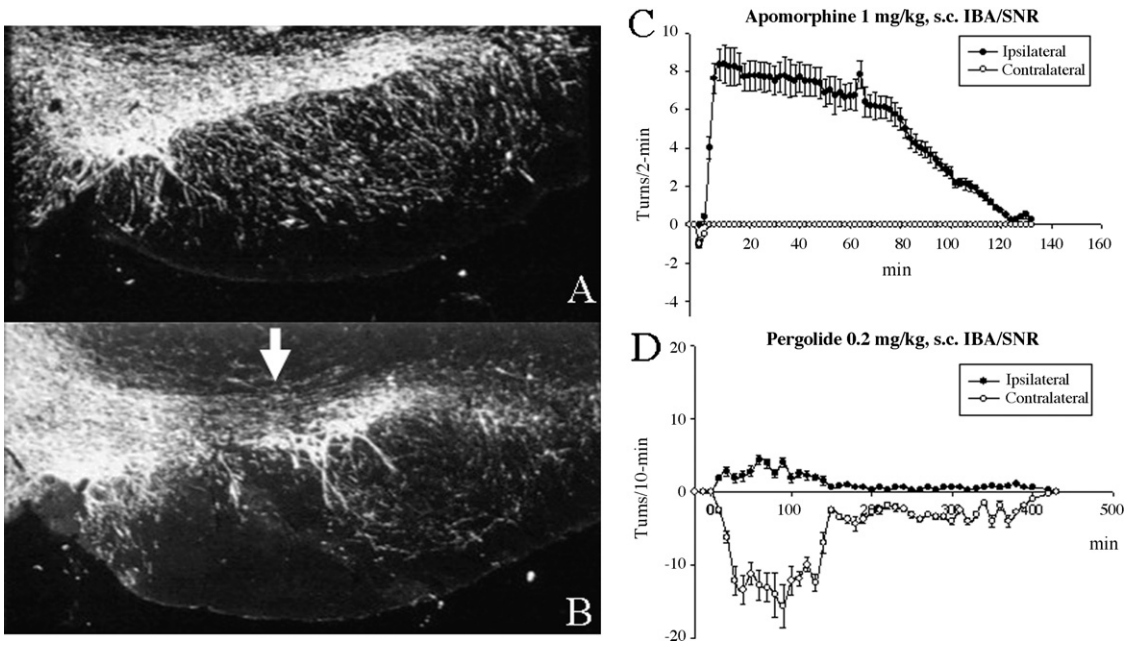

Fig. 5. (A–D) A, B: Microphotographs of tyrosine hydroxylase immunocytochemistry of control (A), and ibotenic acid-lesioned (B) substantia nigra. Ibotenic acid (2.5 μg/0.5 μl) was stereotaxically injected into the left substantia nigra pars reticulata (coordinates: B-5.8, L-2.0, V-8.5; according to atlas of Paxinos and Watson, 1986). Immunocytochemistry revealed a substantial loss of immunoreactive dendrites in the substantia nigra pars reticulata, and some restricted loss of dopamine cells in the pars compacta (arrow) (cf. A versus B) (see Herrera-Marschitz et al., 2007). C, D: Rotational behaviour produced in rats with a unilateral ibotenic acid–lesion of the substantia nigra, pars reticulata (IBA/SNR). The same lesioned rats rotated ipsilaterally following apomorphine (APO; 1.0 mg/kg, s.c.; $n = 6$) (C); but contralaterally following pergolide (0.2 mg/kg, s.c.; $n = 6$) (D). Abscissa: min after drug administration. Ordinate: turns/10 min (positive counts = ipsilateral; negative counts = contralateral). Vertical lines show S.E.M. (from Herrera-Marschitz, 1986; see Herrera-Marschitz et al., 2007).

(^{3}H-spiperone binding), but not for D_1 receptor (DA-stimulated adenylate cyclase) assays. A breakthrough was provided by the discovery of the first selective D_1 antagonist, the benzazepine SCH 23390 (Iorio et al., 1983) and its rapid characterisation by J. Hyttel in Denmark (Hyttel, 1983), who generously provided us with some few milligrams of the drug to be tested in our models (Herrera-Marschitz et al., 1984; Herrera-Marschitz and Ungerstedt, 1985).

7.6. D_1, D_2 receptor families

There are, however, several DA receptors, classified in two families, the D_1 family comprising the D_1 and D_5 receptor subtypes, and the D_2 family, comprising the D_2, D_3 and D_4 receptor subtypes. All subtypes are expressed in the basal ganglia of the rat, with extensive overlapping, but also with some specific regionality (see Bentivoglio and Morelli, 2005). The D_1 and D_2 receptors are usually similarly distributed, although expressed by different neuronal populations. The unique postsynaptic location of D_1 receptors in substantia nigra, pars reticulata, is however remarkable; whereas in substantia nigra, D_2 receptors are expressed by dopamine neurons. The particular distribution of D_1 and D_2 dopamine receptors may explain some of the results shown here, but we do not have any suggestion about how other DA receptor subtypes may be involved in the rotational behaviour elicited by different DA agonists in 6-OHDA-lesioned rats (see Robertson, 1992).

7.7. D_3 receptors and the two-component hypothesis of rotational behaviour

While less prominently distributed, D_3 receptors are particularly over represented in limbic areas, perhaps conveying the rotational behaviour elicited by pergolide or quinpirole, also a D_3 receptor agonist. Indeed, D_3 receptor binding and gene transcripts are expressed by medium-sized neurons in the rostral pole and ventromedial region of the nucleus accumbens (Diaz et al., 1995); a possible explanation for the two-component hypothesis of rotational behaviour proposed by Pycock and Marsden (1978). According to that hypothesis, rotational behaviour would imply a postural deviation and a stereotypy component, both triggered by the neostriatum, and a locomotion component triggered by the accumbens. Perhaps, the locomotion component is conveyed by D_2/D_3 DA receptors preferentially expressed in nucleus accumbens. D_4 and D_5 receptor subtypes are probably not directly involved with rotational behaviour, because, while sparsely distributed, they are specifically over represented in neocortex (D_4) and hippocampus (D_5) (Bentivoglio and Morelli, 2005).

8. Regulators of G-protein signalling (RGS) as intracellular modulators of dopamine receptors

8.1. Modulation of DA receptors by RGS proteins

The coupling of DA receptors to guanine nucleotide binding (G) proteins is regulated by proteins acting as GTPases. RGS proteins activate or deactivate the breakdown of guanine triphosphate (GTP), transiently bound to G-protein subunits, modulating the action of agonists (see Neubig and Siderovski, 2002) and antagonists (Taymans et al., 2004) to G protein-coupled receptors (see McGinty et al., 2008). Several RGS protein subfamilies have been characterised, based on structural features and specificity for different G-protein subunits (Traynor and Neubig, 2005).

8.2. Gaiting basal ganglia outflow by RGS proteins

RGS proteins represent alternative pathways gating the flow of information generated in the basal ganglia. The isoforms RGS2, 4, 8, 9 and 10 have been reported to be associated to nigrostriatal and mesolimbic dopaminergic pathways, with RGS2 preferentially co-localised with D_1 receptors and RGS4 and RGS9 with D_2 receptors. RGS2, 5 and 8 are upregulated, while RGS4 and 9 subfamilies are

downregulated following a 6-OHDA lesion (Geurts et al., 2003). It is not known yet, how up- or downregulation of these proteins affect rotational behaviour, but RGS proteins have been proposed to play a role in long-term adaptation processes, including those leading to neurodegenerative diseases (Tekumalla et al., 2001).

8.3. Upregulation and downregulation of RGS proteins by DA agonists

Based on an elegant series of experiments, Taymans and collaborators (Taymans et al., 2004) showed that the DA D_1 agonists, SKF 82958 and SKF 38393 increased RGS2 mRNA expression in the striatum ipsilateral to a 6-OHDA lesion, up to 10-fold when compared to the effect of the same treatment in normal rats. The selective $D_{2/3}$ agonist quinpirole increased instead RGS4 mRNA expression. These experiments support the idea that DA transmission is a subject of multiple regulation, associated to the expression and activity of different receptor subtypes, and further through different intracellular metabolic cascades modulating the final outcome of basal ganglia neurocircuitries. It is still unclear, however, whether this differential regulation relates to functional and neuropathological conditions, including those assessed by the rotational behaviour paradigm.

8.4. Coupling and decoupling of DA receptors modulated by RGS proteins

Via alternative splicing of the RGS9 gene, two products are yielded, RGS9-1 and RGS9-2, displaying highly specific, non-overlapping tissue distribution. RGS9-1 is expressed exclusively in the retina, while RGS9-2 is expressed in the neostriatum, particularly in medium spiny projection neurons (Thomas et al., 1998). It has been shown (Rahman et al., 2003) that apomorphine produces ipsilateral rotation following unilateral viral-mediated (herpes simplex) overexpression of RGS9-2 in rat nucleus accumbens, suggesting a hemisphere imbalance regarding dopaminergic neurotransmission due to the unilateral overexpression of RGS9-2, antagonising the effect of apomorphine. No rotational behaviour was observed when RGS4 was over expressed, but a similar degree of apomorphine-induced ipsilateral rotational behaviour was observed following overexpression of the RGS9-1 product. That effect was also observed following systemic quinpirole, but not SKF 81297, treatment indicating that the effect of RGS9-2 overexpression on dopaminergic neurotransmission is selective for D_2 receptor. However, both quinpirole and SKF 81297 produced rotational behaviour following RGS9-1 overexpression (Rahman et al., 2003). That observation is intriguing. RGS9-1 and RGS9-2 are produced by alternative splicing from the same gene, differing in only their C-terminus. RGS9-1 has an 18 residue C-terminus, while RGS9-2 has a 205 residues extend C-terminus (Zhan et al., 1999). Thus, differences in the C-terminus should be enough for coupling/decoupling D_1 and/or D_2 receptors. How this mechanism works for multiple DA receptor subtypes, segregated between striatonigral and striatopallidal pathways, remains to be investigated.

9. Clinical microdialysis: a translational venture

The development of microdialysis as a general tool for studying tissue and organ chemistry has led to a truly translational venture as microdialysis is brought into clinical use. Out of the 12,000 papers published using microdialysis about 2000 concern the use in human tissues and organs. Taking our studies into the human domain is a logical and necessary step considering the rapid development of the biochemical knowledge. We cannot limit ourselves to monitoring physical variables in the clinic or relying on clinical observations at the same time as we spend a great amount of our time studying and researching the chemical pathology of the tissues and organs.

Today there are microdialysis catheters available for implantation in brain, abdomen, liver, muscle, subcutaneous tissue and intravenously. There are miniature perfusion pumps, microvials and analysers suitable for intra operative as well as bedside use in the *Intensive Care Unit*. Tissue chemistry data are presented as trend curves on bedside monitors together with physiological data in order to help the staff to decide about treatment and to evaluate the effect of their interventions in real time.

Microdialysis monitors the environment of the cells regardless of whether the substances are produced from the cells themselves or imported from the local capillary blood flow. It samples the environment that tells us if the cells are functioning normally, whether they are being supplied normally with the required metabolic substrates, the drug concentrations they are exposed to and the pathology they are suffering, and we can sample the cellular environment whether the cells are inside or outside the blood brain barrier (see Ungerstedt, 1991).

In case of energy metabolism deficits (Fig. 6) it is of obvious value to sample glucose metabolism using markers such as glucose, lactate and pyruvate where the lactate/pyruvate ratio is a well known marker of the redox state of the tissue and an indicator of tissue ischemia. An important aspect of the lactate/pyruvate ratio is that changes in catheter recovery, e.g. due to tissue oedema, or changes in the flow of the perfusate through the catheter do not affect the ratio. Therefore, this ratio is useful for comparing one organ to another organ or one patient to another patient, and for estimating the degree of ischemia (Reinstrup et al., 2000).

Another valuable feature of the lactate/pyruvate ratio is that increases in lactate due to an increase in cell metabolism are not misinterpreted as a sign of ischemia as long as the lactate/pyruvate ratio remains the same. Furthermore, the lactate/pyruvate ratio tells us if a decrease (or increase) in tissue oxygen has a real effect on cell metabolism. The tissue level of oxygen is dependent upon the supply from capillaries, and the true impact on cell pathology can only be understood by analysing the lactate/pyruvate ratio, i.e. the change in cell metabolism that may or may not follow a change in tissue oxygen.

Once there is an increase in the lactate/pyruvate ratio we want to know if this is damaging to the cells. Cells may react differently to changes in their redox state depending on the type of cell as well as the degree of pathology affecting the investigated tissue. We can then use indirect markers of cytotoxicity such as glutamate (Nilsson et al., 1999) or a direct marker such as glycerol (Hillered et al., 1998). Cell membranes are largely built from glycero-phospho-lipids and

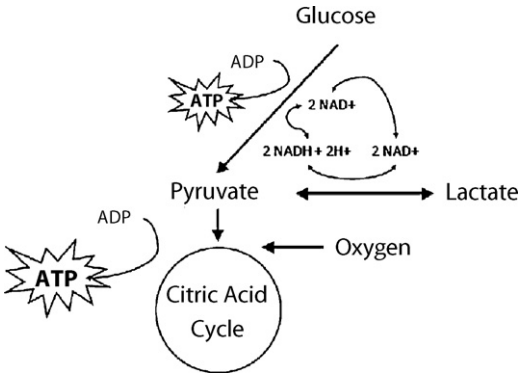

Fig. 6. Schematic diagram of glucose metabolism. Pyruvate is the end-product of glycolysis in tissues with mitochondria and an adequate supply of oxygen. Under anaerobic conditions, pyruvate can be reduced by NADH to form lactate. The conversion of glucose to lactate by anaerobic glycolysis allows the continued production of ATP in tissues that lack mitochondria or in cells deprived of oxygen.

when they are under attack from phospholipases glycerol is released as a sign of membrane decomposition.

In adipose tissue, however, glycerol is a marker of lipolysis (Arner et al., 1988) controlled by the local supply of sympathetic nerves. This means that glycerol may serve as an important indirect marker of sympathetic stress once a microdialysis catheter is inserted subcutaneously in the patient. This is still a largely unexplored application of microdialysis and of potential great value in the intensive care setting!

The interest in inflammatory processes in a number of clinical conditions such as brain trauma, sepsis and transplant rejection has led to microdialysis of inflammatory mediators such as cytokines (e.g. tumour necrosis factor (TNF)-a, interleukin (IL)-1b, IL-6 and IL-10a, 17–28 kDa) and chemokines (IL-8, MCP-1, IP-10 and MIG; m.w. 7–11 kDa). This has become possible when using microdialysis catheters with large pore membranes and a molecular cut off of 100.000 Da or higher (Hillman et al., 2006).

Furthermore, microdialysis emerges as a truly unique tool for monitoring the free fraction of drugs in catheters placed in tissues and organs or in the blood using intravenous microdialysis catheters. It becomes possible to evaluate the penetration of drugs over the blood brain barrier both when it is intact and when it is damaged (Bouw et al., 2001) and the extent to which, e.g. antibiotics reach an infected organ. In the future we may envision the possibility to estimate the pharmacokinetic variables as well as the pharmacodynamic responses in an individual patient and in this way optimize our drug treatment to match the pathological process.

Finally, there are instances when microdialysis may be used to administer exogenous or endogenous compounds to an individual tissue or organ. An isotope such as ^{13}C labelled glucose may be included in the perfusate with the aim of studying glucose metabolism in the tissue (Gustafsson et al., 2007) or the tissue or organ may be fed with a substrate of an important enzyme reaction while recovering the product through the same microdialysis catheter. This may become especially interesting when used to evaluate the pathological state of the liver resection during cancer surgery and when harvesting a liver from a donor.

The vision of clinical microdialysis is easy to understand: We want to detect pathological changes before we see them as clinical signs. Ideally we even want to detect those processes that eventually may lead to pathology. All of this comes down to the important fact that we need more time in order to successfully intervene in a clinical situation.

It seems reasonable to assume that tissue and organ pathology starts with changes in tissue biochemistry—even when the primary damage may be physical—as in traumatic brain injury. We want to avoid the secondary damage whether it is due to ongoing chemical processes in the cells or due to the nature of our pharmacological and surgical interventions.

Already at the present stage of the microdialysis technique, it is beyond doubt that we can detect pathological changes in tissue chemistry before we detect changes in clinical signs. Vasospasm after subarachnoid haemorrhage (SAH) is detected by changes in the lactate/pyruvate ratio on an average 11 h before clinical signs as measured by transcranial Doppler (Skjoth-Rasmussen et al., 2004). Ischemia in a free flap is detected as soon as a thrombosis compromises the capillary flow to such an extent that tissue ischemia develops (Udesen et al., 2000). This early detection of flap ischemia gives the surgeon 5–6 h to intervene and remove the thrombus.

With ongoing research we will increase our understanding of the pathological processes behind events such as ischemia, vasospasm, thrombus formation and inflammation. We can intervene even earlier and thus increase the size of our window of opportunities. Above all we can monitor the impact of our interventions aiming to restore the normal physiology and chemistry of the tissue.

10. Conclusions

The detailed anatomy of the monoamine pathways of the rat provided the basis for a pharmacology targeting to specific neurocircuitry, leading to important therapeutic breakthroughs. Progress was achieved by identifying selective neurotoxins to perform discrete lesions of neuronal pathways of the CNS. The 6-OHDA rotational model provided a powerful method for screening drugs useful for alleviating Parkinson's disease and other DA-related diseases. When combined with *in vivo* microdialysis, the rotational model allows identification of pre- and postsynaptic mechanism of action on DA synapses. The model was useful for demonstrating the role of DA receptors, gating the flow of information from neostriatum through different efferent pathways; the striatopallidal system, via D_2 receptors, and the striatonigral system, via D_1 receptors. The role of other DA receptor subtypes on rotational behaviour has not yet been clarified. The coupling of DA receptors to different G proteins is regulated by a number of proteins (RGS) acting as GTPases. There is a regional segregation in the expression of different RGS in the rat brain (Gold et al., 1997), and specific cell types (see Neubig and Siderovski, 2002). RGS2 has a unique transcriptional responsiveness to neuronal excitation, and is preferentially co-localised with D_1 receptors, while RGS4 and RGS9 are co-localised with D_2 receptors. The specific segregation of this type of proteins supports the idea that the effect of endogenous dopamine is conveyed through multiple dopamine receptors, but there is also an intracellular modulation, coupling or decoupling different metabolic cascades via alternative neuronal pathways.

The development of microdialysis as a general tool for studying tissue and organ chemistry has led to a truly translational venture as microdialysis is brought into clinical use. Today there are microdialysis catheters available for implantation in different tissues, together with miniaturized pumps, microvials and analysers suitable for intra operative as well as bedside use in the *Intensive Care Unit*. Microdialysis monitors the environment of the cells regardless if the substances are produced from the cells themselves or imported from the local capillary blood flow. It samples the environment that tells us whether the cells (i) are functioning normally; (ii) are supplied normally with the required metabolic substrates; (iii) are receiving the expected drug concentration, or (iv) are exposed to other pathological conditions; sampling the cellular environment regardless of whether the cells are inside or outside the blood brain barrier. Microdialysis is a useful technique for monitoring energy metabolism following global or focal ischemia, in the neurosurgery or systemic diseases scenario. With ongoing research, microdialysis will provide information anticipating the clinical outcome, making it possible to intervene earlier, increasing the therapeutic window. Above all we will be able to monitor the impact of our interventions aiming to restore the normal physiology and chemistry of the tissue.

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