On the Origin of Cortical Dopamine: Is it a Co-Transmitter in Noradrenergic Neurons?

Paola Devoto* and Giovanna Flore

"B.B. Brodie" Department of Neuroscience, University of Cagliari, Cagliari, Italy

Abstract: Dopamine (DA) and noradrenaline (NA) in the prefrontal cortex (PFC) modulate superior cognitive functions, and are involved in the aetiology of depressive and psychotic symptoms. Moreover, microdialysis studies in rats have shown how pharmacological treatments that induce modifications of extracellular NA in the medial PFC (mPFC), also produce parallel changes in extracellular DA.

To explain the coupling of NA and DA changes, this article reviews the evidence supporting the hypothesis that extracellular DA in the cerebral cortex originates not only from dopaminergic terminals but also from noradrenergic ones, where it acts both as precursor for NA and as a co-transmitter.

Accordingly, extracellular DA concentration in the occipital, parietal and cerebellar cortex was found to be much higher than expected in view of the scarce dopaminergic innervation in these areas.

Systemic administration or intra-cortical perfusion of α_2-adrenoceptor agonists and antagonists, consistent with their action on noradrenergic neuronal activity, produced concomitant changes not only in extracellular NA but also in DA in the mPFC, occipital and parietal cortex.

Chemical modulation of the locus coeruleus by locally applied carbachol, kainate, NMDA or clonidine modified both NA and DA in the mPFC.

Electrical stimulation of the locus coeruleus led to an increased efflux of both NA and DA in mPFC, parietal and occipital cortex, while in the striatum, NA efflux alone was enhanced.

Atypical antipsychotics, such as clozapine and olanzapine, or antidepressants, including mirtazapine and mianserine, have been found to increase both NA and DA throughout the cerebral cortex, likely through blockade of α_2-adrenoceptors. On the other hand, drugs selectively acting on dopaminergic transmission produced modest changes in extracellular DA in mPFC, and had no effect on the occipital or parietal cortex.

Acute administration of morphine did not increase DA levels in the PFC (where NA is diminished), in contrast with augmented dopaminergic neuronal activity; moreover, during morphine withdrawal both DA and NA levels increased, in spite of a diminished dopaminergic activity, both increases being antagonised by clonidine but not quinpirole administration.

Extensive 6-hydroxy dopamine lesion of the ventral tegmental area (VTA) decreases below 95% of control both intra- and extracellular DA and DOPAC in the nucleus accumbens, but only partially or not significantly in the mPFC and parietal cortex.

The above evidence points to a common origin for NA and DA in the cerebral cortex and suggests the possible utility of noradrenergic system modulation as a target for drugs with potential clinical efficacy on cognitive functions.

INTRODUCTION

Cognitive functions such as working memory, attention and executive tasks are mainly dependent on frontal cortex activity, the performance of which is modulated by dopamine (DA) and noradrenaline (NA). These catecholamines exert a biphasic effect on cognitive functioning, determining an inverted-U shaped dose-curve, normal cognitive operation occurring only within a limited range of dopaminergic and noradrenergic activity [7, 8, 47, 73, 82, 125]. Consequently, imbalances in dopaminergic and noradrenergic system functioning are involved in the aetiology of different psychiatric diseases such as schizophrenia, ADHD and depressive illness [13, 39, 56, 85, 126, 128].

The cerebral cortex receives dense and widespread noradrenergic innervation, whereas dopaminergic terminals are concentrated in the medial prefrontal cortex (mPFC), anterior cingulate, rhinal and entorhinal cortices [23, 69, 102]. However, DA receptors are not confined to the innervated regions, but instead are widely spread throughout the cerebral cortex [45, 67, 71, 97, 121]. Moreover, cortical tissue NA concentrations exceed those of DA even in regions with overlapping dopaminergic and noradrenergic innervations, such as the mPFC [35].

*Address correspondence to this author at "B.B. Brodie" Department of Neuroscience, Cittadella Universitaria, SS 554, km 4,500, I-09042 Monserrato (CA), Italy; Tel: +39-070-6754344; Fax: +39-070-6754320; E-mail: pdevoto@unica.it

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Experimental evidence indicates a coupling between NA and DA release in the PFC [62], and different conditions including stress [36, 37, 61, 83], antidepressants [29, 76, 114], psychostimulants [22, 98] antipsychotic drugs [27, 66, 91, 123], α_2 adrenoceptor agonists and antagonists [24, 28, 50, 62] have been shown to produce concomitant changes in extracellular DA and NA in the PFC. To explain these parallel changes in extracellular NA and DA concentration, the "heterologous uptake" hypothesis has been formulated: indeed, plasma membrane monoamine transporters lack selectivity for their substrates, and the uptake transporters DAT, NET and SERT, in spite of their exclusive expression in neurons that, respectively, synthesise and release DA, NA or serotonin, also accumulate monoamines released from different neuronal systems [15, 80, 115, 119]. Moreover, NET displays higher affinity for DA than for NA *in vitro* [58, 95], and DAT is scarcely expressed in the mPFC [21, 107], while NET and SERT are well represented [77, 103]. Even though NET expressing fibres are generally separated from dopa-minergic neurons and they never contact the same dendritic structures [78], DA and NA can interact through extra-synaptic process, being diffused by volume transmission [81, 132]. As a consequence of these observations, it is likely that in the cerebral cortex, a consistent fraction of extracellular DA is recaptured by NET into noradrenergic terminals. Thus, it has been postulated that in the mPFC, parallel increases of DA and NA are due to competition for the same transporter; accordingly in some circumstances, DA increase might be the passive consequence of increased extracellular NA [15, 80, 93, 127]. However, data from our laboratory, as well as from other groups, indicate that DA, in addition to being recaptured, is also released with NA from noradrenergic terminals, being not only a precursor but also a co-transmitter of NA in the cerebral cortex.

EXTRACELLULAR CATECHOLAMINE CONCENTRATIONS

Our studies are conducted by means of cerebral microdialysis in freely moving animals. This technique provides for an implant in specific cerebral areas of probes constructed using semi-permeable membrane, through which an artificial cerebral spinal fluid is constantly circulated, allowing exchange of substances with extracellular fluid along concentration gradients. This method facilitates the collection of neurotransmitters, or the administration of drugs, over a well circumscribed area of the brain.

In cerebral areas such as the parietal and occipital cortex and the cerebellum, we observed that extracellular DA levels are higher than expected from their scarce or absent dopaminergic innervation, and are fairly similar to the level found in the prefrontal cortex, which receives a dense dopaminergic innervation [24]. We confirmed our early data, obtained by transversal microdialysis, by means of experiments performed by vertical probes [31, 32]. However, others [118] have reported DA levels in occipital and parietal cortex lower than those they found in the prefrontal cortex. Because the main difference between these experiments is in the anaesthetic used, perhaps the anaesthesia with ketamine [118] or Equithesin (our conditions) could differentially affect basal DA levels in the cortex, even hours after administration. Indeed, it has been demonstrated that ketamine anaesthesia causes a significant decrease in cortical extracellular level of glutamate and other excitatory aminoacids, while Equithesin has no significant effect [101].

Table **1** shows extracellular concentrations of NA, DA and its main metabolite DOPAC, determined in the same conditions in the mPFC, parietal and occipital cortex and in the nucleus accumbens, which receives a preponderant dopaminergic innervation. Correspondent probe positions are schematically depicted in (Fig. (**1**)).

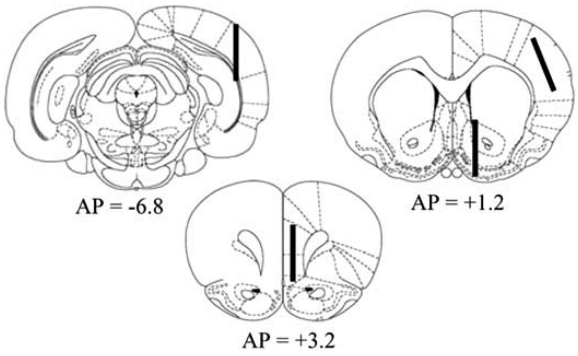

Fig. (1). Schematic representation of probe positioning in the mPFC (A=+3.0), the parietal cortex and the nucleus accumbens (A=+1.2), and the occipital cortex (A=-6.8), according to [89].

Consistent with the homogeneous noradrenergic innervation, NA levels are very similar in the three cerebral cortices but, quite surprisingly, no significant difference exists among cortical DA values. On the other hand, DOPAC concentrations decrease from mPFC to occipital cortex, each concentration differing significantly from the others.

Extracellular DOPAC concentration mostly originates from intracellular catabolism of newly synthesised DA, thus

Table 1. Extracellular NA, DA and DOPAC Concentrations in Different Rat Brain Areas

Cerebral area	NA	DA	DOPAC
Medial prefrontal cortex (163)	3.1 ± 0.2	2.8 ± 0.2	188.2 ± 11.1
Parietal cortex (64)	3.0 ± 0.2	2.3 ± 0.1	122.7 ± 17.7
Occipital cortex (11)	3.8 ± 0.5	2.6 ± 0.3	12.9 ± 1.7
Nucleus Accumbens (19)	9.0 ± 1.0	59.1 ± 10.4	2494.2 ± 221.5

Values are the means ± SEM of data obtained in the number of rats indicated in parenthesis, and are expressed as pg/sample injected on column.

it could be considered as an index of dopaminergic neuronal activity [110, 130]. In this regard, it should be underlined how the highest DOPAC value was found in the prevalently dopaminergic nucleus accumbens, where DA level is more than 20 times higher than in the cortices, according to a concentration gradient strictly resembling the intensity of dopaminergic innervation. Even though DOPAC must be taken into account just as an indirect measure of dopaminergic activity, the extracellular concentration of DOPAC, rather than DA, seems to reflect the presence of dopaminergic innervation.

Since dopaminergic innervation of the cerebral cortex is maximal in the mPFC and minimal or absent in the parietal and occipital cortex [23, 69], the equal and relatively high levels of extracellular DA in these cortical areas are intriguing and suggest that DA might originate from non dopaminergic neurons. Indeed, this DA is neuronal in origin, as its release is increased following membrane depolarisation by local perfusion of high concentration of K^+, and decreased by Na-channel blocking, by means of tetrodotoxin local perfusion [24, 30, 31].

It could be hypothesised that DA found in scarcely innervated cortical areas originates from areas where DA neurons are present and diffuse throughout the cortex. Indeed, DAT expression is very scarce in the cerebral cortex, and DA diffusion is strictly correlated to DAT activity [107]. Thus, the relatively high extracellular DA levels could be due to its diffusion, secondary to low DAT presence. However, even though DA volume transmission is likely to occur [132], long-distance diffusion of DA should be limited by NA transport system which, as already stated (see above), actively re-uptakes DA and is well represented throughout the cerebral cortex.

NORADRENERGIC DRUGS

Being the precursor of NA, DA is synthesised by tyrosine hydroxylase not only in dopaminergic but also in noradrenergic neurons, in whose synaptic vesicles it is converted into NA by dopamine-β-hydroxylase. Kinetic studies suggest that the rate of NA production could be much slower than the uptake of DA into vesicles [5]. Thus, we hypothesise that DA is not totally turned into NA, and is co-released with NA from noradrenergic terminals. If this hypothesis is true, then drugs affecting noradrenergic function must also influence extracellular DA levels in the cerebral cortex.

The α_2-agonist clonidine, through activation of auto-receptors, inhibits noradrenergic neuronal activity and NA release [3]. Clonidine produces a dramatic decrease in extracellular levels not only of NA but also of DA throughout the cerebral cortex, after systemic administration [24, 27] (Fig. (**2**)) and after local perfusion into terminal areas [24] or into the locus coeruleus [26, 62], from which cortical noradrenergic innervation originates. Furthermore, after local inhibition of uptake by desipramine perfusion, clonidine administered into the locus coeruleus maintains its ability to reduce cortical DA: thus, DA decrease is not the consequence of augmented re-uptake, but of reduced release [26]. Clonidine perfusion into the locus coeruleus does not affect extracellular DA in the ventral striatum, decreasing only NA concentration in this area [26]. This observation is consistent with the prominent dopaminergic innervation of the ventral striatum and argues against a tonic stimulation of VTA dopaminergic cells by NA. Locus coeruleus noradrenergic neurons project on dopaminergic perikaria, where through postsynaptic α_1-adrenoceptors, NA might influence the firing rate of dopaminergic neurons [6, 48] leading to an

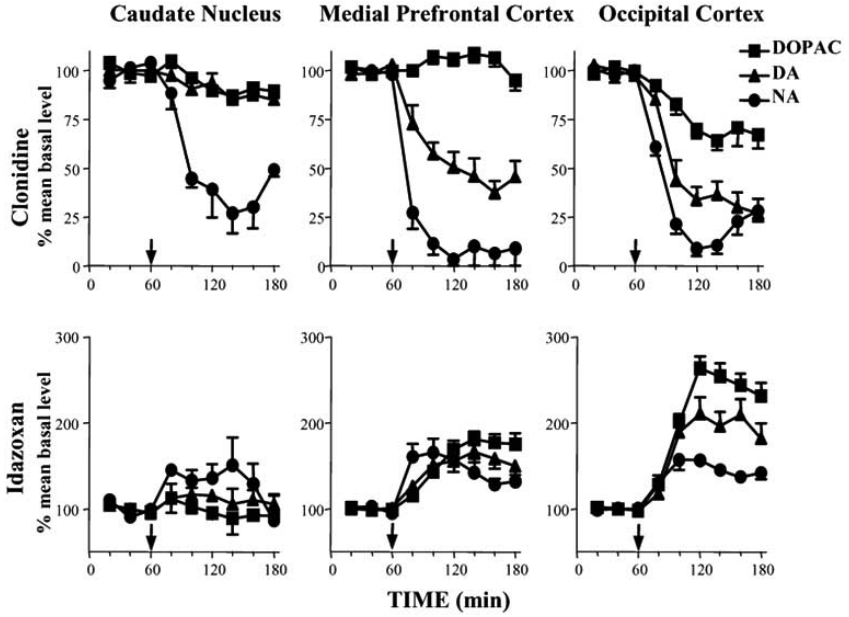

Fig. (2). Effect of systemic administration of clonidine (0.15 mg/kg i.p., upper panel) or idazoxan (15 mg/kg i.p., lower panel) on extracellular levels of NA, DA and DOPAC in the caudate nucleus, mPFC and occipital cortex. Arrows indicate time point of drug administration.

increased response to other excitatory afferents [3, 4]. It has been shown that clonidine, systemically administered, elicits a regularising action on VTA dopaminergic neurons, while α_2-antagonists produce deregularisation and increase of firing [49], thus generating a decrease and an increase, respectively, of DA release in terminal areas [46]. Midbrain dopaminergic neurons do not express α_2-adrenoceptor mRNA [104], thus these drugs should act through α_2-adrenoceptor located on non-dopaminergic neurons in the midbrain [52, 104, 117].

Indeed, noradrenergic effects on DA neuron electrical activity have been hypothesised to be mediated by an indirect effect requiring catecholamine release [49, 88].

There is no unequivocal *in vivo* evidence for the existence of a tonically active noradrenergic input to midbrain DA neurons [49], and recently, *in vitro* evidence of a direct inhibition, rather than excitation, of the activity of dopaminergic cells by NA has been provided [87].

Alpha$_2$-adrenergic antagonists, such as idazoxan and RS 79948, increase not only NA, but also DA and DOPAC, after systemic administration or local perfusion into medial prefrontal, parietal and occipital cortex [24, 28, 62] (Fig. **2**), while in the caudate and accumbens nuclei only NA, and not DA, is affected by idazoxan [57, 112] (Fig (**2**)). Moreover, perfusion of the ventral tegmental area with tetrodotoxin, which reduces cortical output of DA, does not prevent idazoxan ability to enhance DA efflux in the PFC [57], and idazoxan is still active in increasing cortical DA level in rats lesioned with 6-hydroxy dopamine (6-OHDA) into the medial forebrain bundle [112]. On the other hand, when perfused into the VTA, idazoxan fails to increase cortical DA level, thus arguing against a tonic inhibition of dopaminergic cells by NA *in vivo* [57]. These findings indicate that α_2-adrenergic effects on cortical DA efflux are independent from neuronal activity of VTA dopaminergic cells.

Changes in extracellular DA produced by α_2-adrenoceptor ligands might be mediated by α_2-heteroreceptors located on dopaminergic terminals [59, 129]. However, several considerations argue against this interpretation:

a) α_2-adrenoceptor agonists and antagonists affect DA efflux not only in the mPFC but also, and to a greater extent in the occipital cortex, where DA terminals are scarce [24, 28, 29, 118] (Fig. (**2**)).

b) α_2-agonists and antagonists have no or only a scarce effect on DA levels in two brain regions with dense dopaminergic innervation, the nucleus accumbens and the caudate nucleus, in spite of the presence of α_2-adrenoceptors [57, 112] (Fig. (**2**)).

c) The effect of α_2-adrenoceptor antagonists on DA release in the mPFC is suppressed by lesion of the dorsal noradrenergic bundle [118] and not of the medial forebrain bundle [112].

d) No α_2-adrenoceptor mRNA has been detected in midbrain dopaminergic neurons [104].

STIMULATION OF LOCUS COERULEUS

Noradrenergic neuronal activity can be modulated by perfusion of locus coeruleus with specific drugs, as described previously for clonidine, the inhibitory action of which is manifested by a profound decrease in cortical levels of both NA and DA [26, 62]. Stimulation of locus coeruleus neuronal activity by local perfusion with the glutamate agonists NMDA and kainate, or the muscarinic receptor agonist carbachol, or the GABA antagonist bicuculline, elicits parallel increases of both NA and DA in the PFC, while in the nucleus accumbens, extracellular DA remains unchanged [62]. Furthermore, systemic administration of α_1-adrenoceptor antagonist prazosin does not modify the effect of carbachol stimulation, thus excluding an indirect effect mediated by tonic NA activity on VTA [62].

Electrical stimulation of the locus coeruleus enhances NA release in the PFC in a frequency-dependent manner [38]. By simultaneous monitoring of NA and DA, we demonstrated that burst stimuli administration into the locus coeruleus increases both catecholamine levels in the mPFC, occipital and parietal cortex, but only NA in the caudate nucleus. These increases are frequency-dependent, are abolished by TTX local perfusion and occur both in freely moving and anaesthetised rats [30, 31]. These findings indicate that in the cerebral cortex, extracellular DA is correlated with noradrenergic neuronal activity.

However, the co-release hypothesis does not exclude that in the mPFC, DA output also originates from dopaminergic neurons. Indeed, cortical DA release can be modulated by intra-VTA drug infusion, and direct stimulation of the VTA by means of infusion of the muscarinic cholinergic agonist oxotremorine elicits an increase in extracellular DA, but not NA, in the PFC [51, 122]. Moreover, selective activation of ascending dopaminergic neurons increases the voltammetric signal identified as DA by fast-scan cyclic voltammetry in the mPFC [43].

ANTIPSYCHOTICS

Antipsychotic drugs are known to stimulate dopaminergic neuron activity, through blockade of both pre- and post-synaptic D_2 receptors [94]. Thus, haloperidol, classical neuroleptic endowed with D_2 receptor antagonist selectivity, is highly effective in increasing nigro-striatal dopaminergic neuronal activity and striatal DA and DOPAC levels [60, 94]. However, despite its efficacy in increasing the activity of antidromically identified meso-cortical DA cells [44], haloperidol produces no effect [24, 29, 44, 55, 63, 90, 127] or only scarce modifications [28, 79, 122] on extracellular DA concentration in the PFC, where it is active in increasing DOPAC concentration only, while in the occipital cortex, neither NA and DA nor DOPAC levels are affected (Fig. (**3**)), [28]. Anyway, this difference could be ascribed to differences in autoreceptor functioning between mesocortical and mesostriatal DA neurons [9, 10, 20, 40].

On the other hand, the new generation antipsychotics, which possess antagonistic activity towards different classes of receptors, affect cortical DA to a greater degree than subcortical levels, this property being claimed to subserve their superior efficacy against negative symptoms of schizophrenia [63, 68, 79, 84, 90, 120, 124]. Atypical antipsychotics are also effective in increasing NA level, in line with their affinity for α-adrenergic receptors [24, 27, 66, 91, 123].

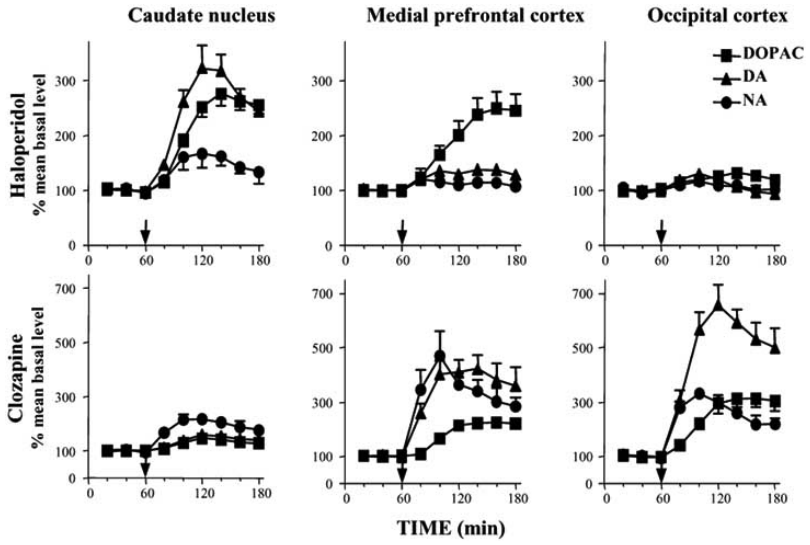

Fig. (3). Effect of systemic administration of haloperidol (0.1 mg/kg i.p., upper panel) or clozapine (10 mg/kg i.p., lower panel) on extracellular levels of NA, DA and DOPAC in the caudate nucleus, mPFC and occipital cortex. Arrows indicate time point of drug administration.

Clozapine, the prototype for atypical antipsychotics, has been the object of extensive investigation. We demonstrated that clozapine augments extracellular NA and DA concentrations not only in the mPFC, which receives consistent dopaminergic innervation, but also, and to a greater extent in the prevalently noradrenergic occipital cortex [27] (Fig. (**3**)). Moreover, both NA and DA increases are completely antagonised by clonidine, while they are not affected by the selective D_2 receptor agonist quinpirole [27]. Clozapine interaction with noradrenergic system has been clearly demonstrated. In fact, it has considerable affinity for a_2-adrenoceptors [14], it increases the firing rate of NA neurons in the locus coeruleus [96] and prevents d-amphetamine-induced suppression of the firing of NA neurons [111]. Nevertheless, clonidine might reverse the effect of clozapine on DA and NA release by an indirect mechanism, or by physiological antagonism. Moreover, due to clozapine interaction with a wide range of receptors [75], induction of NA and DA co-release through different receptor modulation cannot be excluded.

MORPHINE EFFECTS

Morphine elicits opposite actions on VTA dopaminergic- and locus coeruleus noradrenergic-cell activities. Indeed, acute morphine administration inhibits locus coeruleus NA neurons [2] and activates dopaminergic neurons in the VTA [74]. On the contrary, abstinence from chronic morphine is associated with activation of noradrenergic cells [2] and inhibition of VTA dopaminergic neurons [33]. Consistently, extracellular NA levels are decreased by acute morphine and increased by its withdrawal [100, 109], while DA is increased and decreased, respectively, in the nucleus accumbens, one of the projection areas of VTA DA neurons [1, 92]. Quite surprisingly, in the mPFC, which also receives VTA DA projections, extracellular DA levels are not modified by acute morphine administration, and are markedly increased during withdrawal, in spite of the inhibition of VTA DA neuronal activity [12, 25]. We explain this apparent contradiction with the co-release hypothesis [25], basing our conclusion on the observation that in the parietal cortex, which is not innervated by DA, acute morphine administration elicits a parallel decrease in both NA and DA levels, and that when morphine is co-administered with quinpirole to inhibit VTA DA neuronal activity, a DA decrease is evidenced also in the mPFC. Furthermore, the dramatic increase in NA and DA levels elicited in the mPFC of morphine-dependent rats by naloxone, is completely reverted by clonidine, but not quinpirole administration. Again, these findings indicate that in the cerebral cortex, extracellular DA variations better correlate with noradrenergic than with dopaminergic neuronal activity. The apparent lack of acute morphine effect on mPFC DA might be due to the algebraic sum of increase in DA originating from dopaminergic cells and decrease in DA co-released with NA. Alternatively, it might be due to differences in regulation between meso-cortical and meso-limbic DA neurons. Indeed, mesocortical DA system exhibits different functional characteristics with respect to other DA systems [17, 19, 42]. As for the above-mentioned lack of haloperidol effect, differences in autoreceptor [9, 10, 20, 40] or in glutamatergic afferent input [16], might originate different responses to the same stimulus.

VTA LESION

Destruction of striatal dopaminergic innervation by means of 6-OH-DA injection into the substantia nigra/ventral tegmental area has been extensively investigated, being a useful model of Parkinson's disease. DA system has been demonstrated to react to the lesion with numerous compensatory neuroadaptations [131]. It is well known that in the nigro-striatal system, at least 80% depletion of tissue DA is required to observe a small reduction in extracellular DA, while after more than 95% reduction of tissue DA content, extracellular DA also falls below 10% of control

values. Unlike DA, decreases of extracellular DA metabolites are highly correlated with lesion extent and residual tissue content [18, 99].

The comparison of tissue and extracellular DA and DOPAC in the nucleus accumbens and in two cortical areas, the mPFC and the parietal cortex, after monolateral 6-OHDA injection into the VTA [32] may be useful to better elucidate DA origin in the cerebral cortex. To the best of our knowledge, no other similar studies on meso-cortical dopaminergic system have been published.

Table **2** shows that the lesion produces a clear-cut reduction in tissue DA and DOPAC content in all cerebral areas tested, but in the nucleus accumbens, the decrease is more pronounced than in the cortical areas (95% or more versus 50-70%).

Following extensive 6-OHDA lesion of VTA, extracellular DA values are only slightly and not significantly decreased in the mPFC and parietal cortex, but are dramatically reduced in the nucleus accumbens, while extracellular DOPAC decrease corresponds to respective tissue content diminution in all cerebral areas (Table **3**).

Thus, even though dopaminergic innervation of both mPFC and nucleus accumbens originates from the VTA, it appears that cortical areas are less severely affected by 6-OHDA-induced denervation. The relatively high cortical levels remaining in the lesioned side might be due to the presence of DA in noradrenergic neurons. Alternatively, it should be hypothesised that cortical DA originates in part from dopaminergic neurons not arising from VTA, or that meso-cortical dopaminergic neurons may be less sensitive than meso-limbic ones to the effect of 6-OHDA. Even though dopaminergic innervation partly arising from the mediolateral substantia nigra is present in the supragenual cingulate cortex [69], this cortical area has not been included in our study. Indeed, the great majority of dopaminergic terminals in the infralimbic-prelimbic mPFC originate from the VTA [113].

6-OHDA exerts its toxic action after being taken up into neurons by catecholamine transport systems [102], thus neurons devoid of catecholamine re-uptake sites should be protected against lesion. Dopaminergic terminals in the mPFC are known to express fewer DAT with respect to nucleus accumbens innervation [21, 107], however, it is not clear whether this difference is also present in their cellular bodies [108]. If this is the case, then they should be relatively resistant to 6-OH-DA effect.

To date, no experimental evidence has been provided to support either of the aforementioned alternative hypotheses. The only certainty is the presence of DA in noradrenergic neurons innervating the cerebral cortex. Thus, we propose that extensive VTA lesion does not affect extracellular DA in the mPFC and parietal cortex due to being originated prevalently from noradrenergic neurons.

Table 2. Tissue Content of DA and DOPAC in Intact and 6-OHDA Lesioned Cerebral Areas

Cerebral Area	DA		DOPAC	
	Intact	Lesioned	Intact	Lesioned
Medial prefrontal cortex	62.1 ± 3.7	17.7 ± 2.0 28%	38.2 ± 4.0	20.4 ± 4.0 53%
Parietal cortex	15.5 ± 1.5	5.9 ± 0.4 38%	21.6 ± 2.8	12.8 ± 2.4 59%
Nucleus accumbens	5387.2 ± 298.2	173.5 ± 27.5 3%	1652.7 ±120.6	95.8 ± 11.3 5%

Values are expressed as pg/ mg tissue wet weight, and are the mean ± SEM of 50 rats. Rats received monolateral 6-OHDA infusion into the VTA, and intact (controlateral to the lesion) *vs*. lesioned (ipsilateral to the lesion) side are compared.

Table 3. Extracellular Values of DA and DOPAC in Intact and 6-OHDA Lesioned Cerebral Areas

Cerebral Area	DA		DOPAC	
	Intact	Lesioned	Intact	Lesioned
Medial prefrontal cortex (20)	2.4 ± 0.3	1.9 ± 0.2 80%	211.8 ± 48.6	23.9 ± 3.7 11%
Parietal cortex (11)	1.9 ± 0.3	1.6 ± 0.2 84%	158.6 ± 37.8	19.0 ± 3.7 11%
Nucleus accumbens (19)	42.5 ± 7.4	3.5 ± 0.6 8%	2636 ± 371	57.3 ± 13.8 2%

Values are expressed as pg/sample and are the mean ± SEM of the number of rats indicated in parenthesis. Following monolateral 6-OHDA infusion into the VTA, rats were implanted with two probes, one for each cerebral hemisphere, and intact (controlateral to the lesion) *vs*. lesioned (ipsilateral to the lesion) side values are compared.

On the other hand, noradrenergic neuron lesion does not alter basal dialysate DA in the mPFC [15, 93, 118, 127] but affects its response to pharmacological challenges, underscoring an increase in DA following previously ineffective dopaminergic drugs, such as haloperidol [127] or the selective DAT inhibitor GBR 12909 [93], and preventing the increase in DA elicited by clozapine [118]. These results could be attributed to a decreased DA clearance by NA transporter, diminished by the lesion, but they could be also due to the compensatory proliferation of dopaminergic terminals that follows noradrenergic degeneration, as suggested by enhanced dopaminergic mechanisms [53, 54, 70, 116]. In this context, the lack of effect of clozapine on DA, in the mPFC and parietal cortex of NA denervated rats, is particularly indicative [118], suggesting that the increase of DA elicited by clozapine in the cerebral cortex is totally due to clozapine effect on noradrenergic system.

CONCLUSION

The evidence presented in this paper converge towards the possibility that in the cerebral cortex, most of DA originates from noradrenergic neurons, from which DA is co-released together with NA.

In the mPFC, DA acts as a neuromodulator [65, 105], and dopaminergic system is responsible for the fine tuning of the neurons it impinges upon [34, 41, 86]. An optimal dopaminergic tone is required to obtain an appropriate reaction to stimuli, or to cope with challenging situations. DA neuro-modulatory role is particularly relevant for the cognitive control exerted by mPFC. In fact, dopaminergic imbalance in the mPFC has been implicated in virtually all psychopathologies, and mainly in schizophrenia related syndromes. A similar regulatory role has also been attributed to NA, particularly in relation with superior cognitive activities and connected psychopathologies [7, 8, 39, 56, 85, 128]. According to our hypothesis, NA and DA neuromodulation in the cerebral cortex is at least in part supported by a common neuronal origin. In fact, even though dopaminergic cortical targets display a well circumscribed localisation in specific areas, namely the mPFC, anterior cingulate, rhinal and entorhinal cortices [23, 69, 106], noradrenergic innervation is uniformly distributed, supplying a dopaminergic tone throughout the entire cerebral cortex and overlapping with proper dopaminergic innervation. This noradrenergic pool of DA might be massively mobilised during conditions of stress (such as morphine withdrawal), and might be utilised by atypical antipsychotics or antidepressants to buffer insufficient dopaminergic tone in the mPFC. Also in case of loss of dopaminergic neurons (such as in Parkinson's disease), the higher cortical functions might be preserved, thanks to DA co-released with NA. This mechanism may be added to the well known compensations that intervene following dopaminergic neuron loss, such as vigorous sprouting and increase of tyrosine hydroxylase activity in remaining axons, and up-regulation of postsynaptic DA receptors.

In other words, prefrontal cortical function plays such a key role in the organism homeostasis that its neuromodulation is committed to a double control. The noradrenergic system might be involved in DA support in the case of insufficient input, the neuro-modulatory action exerted by DA being reinforced by NA in DA innervated cortical areas, such as the mPFC. At the same time, heterologous uptake of DA by NET might contribute to buffer excessive spread of released DA.

This hypothesis might be related to the actions of drugs endowed with noradrenergic activity, such as atomoxetine, guanfacine or atipamezole [8, 11, 64, 72], as a therapeutic tool to modulate cognitive functions [39].

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