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# Dopamine and behavior: functional and theoretical considerations.

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DOPAMINE AND BEHAVIOR :  
FUNCTIONAL AND THEORETICAL CONSIDERATIONS

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Over the last two decades, mesencephalic dopaminergic neurons have been the subject of extensive investigations. Anatomical, pharmacological and behavioral approaches have all been used in attempts to unravel their function. Dahlström and Fuxe (2) classified these neurons into dopaminergic A9 and A10 groups on the basis of the localization of their cell bodies. It was classically considered that the neurons of the A9 group with their cell bodies in the substantia nigra give rise to the nigrostriatal system, while neurons of the A10 group, with their cell bodies situated in the ventral tegmental area, give rise to the mesolimbic system (40). The projection areas of these neurons have been precised. Thus neurons of the A9 group preferentially innervate the striatum, whereas neurons of the A10 group project to several forebrain structures : neocortical areas such as the prefrontal cortex, suprarhinal cortex, limbic areas such as the amygdala, hippocampus, septum, the nucleus accumbens and the olfactory tubercle which make up the ventral striatum (6, 7, 13, 34, 35). The results of such studies have also suggested that the distinction between the A9 and A10 groups may be artificial. It has, for example, been shown that some parts of striatum are innervated by neurons of the A10 group (7, 34, 35). The neurons of the A9 and A10 groups may in fact form a mediolateral continuum, with the dopaminergic mesencephalic neurons forming a large network which can be subdivided into various neuronal subunits (7, 30, 34, 35).

Much of the interest in these dopaminergic neurons derives from clinical studies which have shown that they may be involved in the etiology of Parkinson's disease (5), and from suggestions that a

dysfunction of these neurons may underly some psychotic states (36, 37). Furthermore, many studies have shown that dopaminergic neurons are the preferential target of many psychoactive drugs. Dopaminergic transmission is markedly affected by psychostimulant agents such as amphetamine, as well as by antipsychotic drugs (43). The behavioral disturbances that are induced by psychoactive drugs raise questions about the relationship between dopaminergic systems and behavior. Many behavioral investigations have used techniques involving blockade of dopaminergic transmission by local injection of dopaminergic agonists or antagonists (42). Involvement of dopaminergic neurons in the behavioral responses of animals have been more clearly demonstrated using selective lesions of the cell bodies of these neurons. For example, it has been shown (41) that lesions of the substantia nigra lead to a state of aphagia, adipsia and hypokinesia. Lesions of the ventral tegmental area lead to major behavioral deficits. The syndrome is characterized by deficits in basic behaviors required for survival, such as maternal (9), hoarding (20) and social behavior (23) in addition to exploratory and locomotor disturbances (10, 23). All these investigations have indicated the involvement of dopaminergic systems in fundamental mechanisms underpinning behavioral adaptation.

#### PERMISSIVE ROLE

The extent of the deficits after lesions of dopaminergic nerve cell bodies have led to two opposite views on the role of these neurons : 1) They may be involved in complex information processing during transfer to the projection areas. The deficits would be a reflection of disturbances in both processing and information transfer. 2) Conversely, dopaminergic neurons may not be involved in transfer of specific information, but could facilitate its integration in the projection areas. Deficits would reflect disruption of dopaminergic modulation of processes occurring in these projection areas.

Results from investigations using lesions in the projection areas favor the second hypothesis. Deficits in cognitive functions have been observed after lesions of the dopaminergic terminals in the prefrontal cortex (32). The animals displayed deficits in a delayed alternation task, which is considered to be a sensitive and selective test of frontal cortical function (8, 26). The results obtained in this task

showed that lesions of the dopaminergic innervation of the frontal cortex induced behavioral disturbances that were similar to those observed after global lesions of this structure (3). Lesions of dopaminergic terminals of the septum was found to be followed by increased emotional reactivity, shown by enhanced sensitivity to frustrative effects. These effects were seen in situations in which the food reward was partially suppressed (38, 39). Similar disturbances have been observed after massive lesions of the septum (14). The two studies mentioned above suggested that the features of the behavioral deficits seen after lesions of the dopaminergic terminals were the same as those observed after lesions of the innervated structure itself. This is also confirmed by studies on lesions of dopaminergic innervation of the nucleus accumbens. This structure has a particular anatomical configuration, it is mainly innervated from limbic structures such as the amygdala and hippocampus (18, 19, 21) and it has projections to the globus pallidus and the substantia nigra (13, 29). These anatomical characteristics suggest that the nucleus accumbens forms an interface between the limbic and striatal sensorimotor systems (27) (Fig.1). Behavioral tests used to investigate the

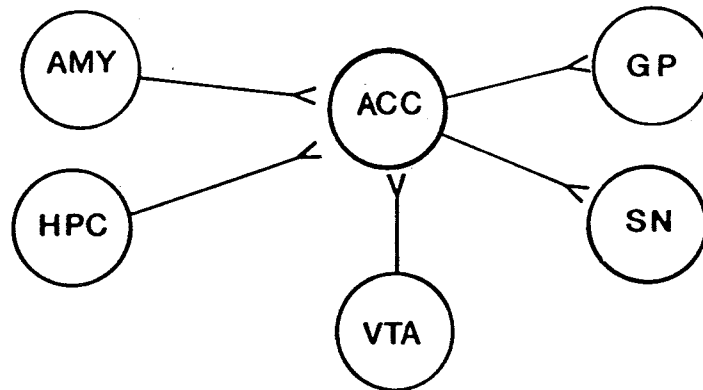


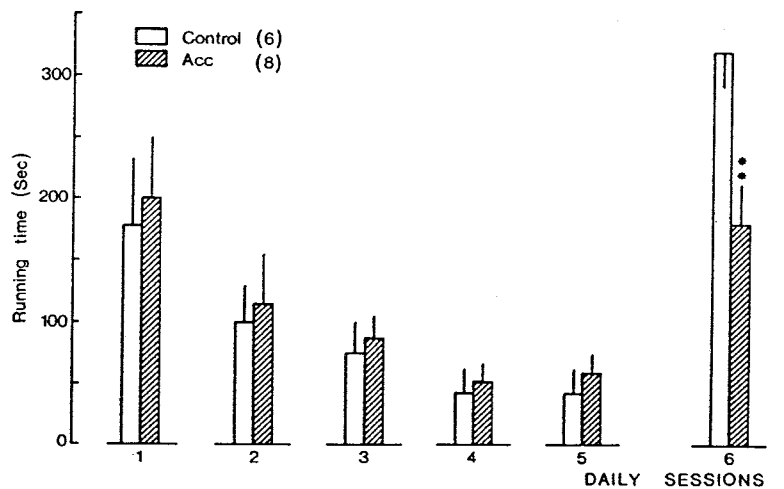
Figure 1 : Schematic diagram of the main afferents and efferents of the nucleus accumbens. AMY: amygdala, ACC: nucleus accumbens, GP: globus pallidus, HPC: hippocampus, SN: substantia nigra, VTA: ventral tegmental area.

effects of lesions of the meso-accumbens demonstrated disturbances in classical striatal sensorimotor and limbic functions.

#### Limbic syndrome

We have used tasks which are widely considered as tests of limbic system dysfunction (15, 17). These tests require behavioral flexibility in switching from one response to another. Two situations were employed using rats with 6-OHDA lesions of dopaminergic terminals in the nucleus accumbens. The first used appetitive reinforcement (straight runway) and the second, aversive reinforcement (passive avoidance task with foot-shock).

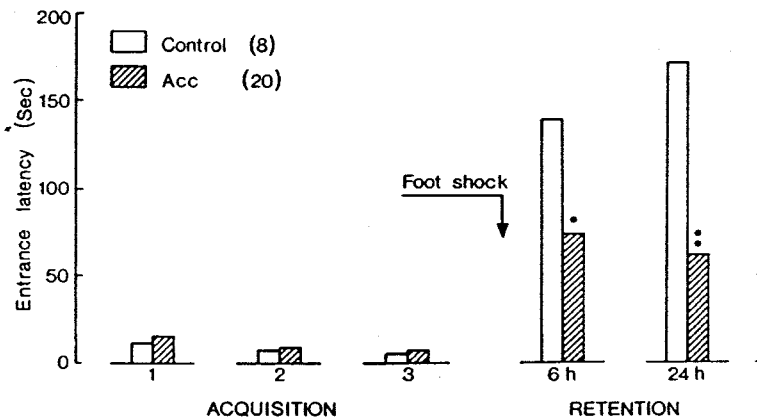
In the first test (Fig.2), food-deprived animals learned to reach a goal box in a 3 meter long runway (6 trials per day for 5 days). Reinforcement consisted of two food pellets. On the 6th day the reinforcement was omitted, and latency to reach the goal box



*Figure 2 : Straight alley test: acquisition and extinction after 6-OHDA injections in the nucleus accumbens. Latency to reach the goal box during the 5 days of the acquisition and the day of extinction (6th day) (mean  $\pm$  SEM). \*\* $p < 0.01$ , Statistical significance with Student's  $t$  test.*

was recorded every day. Although there was no difference between control and experimental groups in the acquisition phase ( $F(1,14) = 0.79$ , NS), on the 6th day during the extinction phase (6 trials), rats with lesions continued to run more rapidly (perseveration) than the controls ( $t(13) = 3.15$ ,  $p < 0.01$ )

In the passive avoidance test (Fig.3) during the three sessions before the foot-shock, the latency to avoid the platform (i.e. to enter the dark compartment) was identical for the two groups. After the foot-shock, the latency was increased in both groups. However, this increase was much less marked in the experimental group, both 6 and 24 h after the foot-shock ( $U = 22$ ,  $p < 0.05$ ; and  $U = 35$ ,  $p < 0.01$ ; Mann-Whitney).



*Figure 3 : Passive avoidance test: acquisition and retention after 6-OHDA injections in the nucleus accumbens. Median latency to enter the dark compartment before and after the footshock. \* $p < 0.05$ , \*\* $p < 0.01$ , Statistical significance with the Mann-Whitney test.*

#### Striatal sensorimotor syndrome

This was evaluated by measuring latency to initiate a behavioral response in three situations (open field, two compartment arena and 4-hole box). In all situations, animals with lesions displayed

increased latency, either to visit the 1st hole in the 4-hole box, to avoid the central square in the open field or to visit the 2nd compartment in the two compartment arena (Fig.4A). However, there was no difference in spontaneous locomotor activity in a circular corridor, during the 1st hour of testing or throughout the 24 h circadian cycle (Fig.4B).

Lesions of dopaminergic innervation of the nucleus accumbens appear to lead to deficits in the initiation of the behavioral response which could be described as a form of perseveration. These disturbances are typically seen after lesions of striatal and limbic structures. In common with studies of the deficits after septal and prefrontal lesions, similar deficits were observed after destruction of the dopaminergic innervation as after lesions of the innervated structure itself.

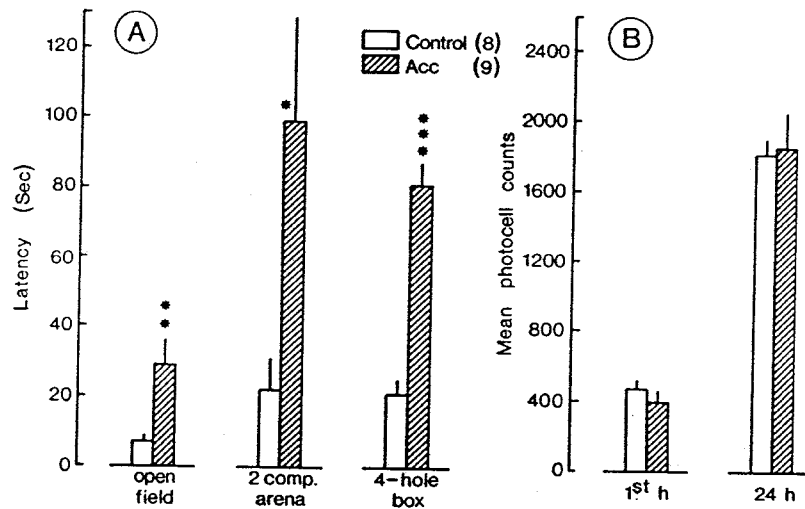


Figure 4 : Effect of 6-OHDA lesions of the dopaminergic terminals in the nucleus accumbens on behavioral initiation and locomotor response. A) latencies to move from the central square of the open-field, to visit the second compartment on the 2-compartment arena and to explore the first hole in the 4-hole test (mean  $\pm$  SEM). B) Photocell counts in circular corridor during the 1st h and 24 h cycle of the test (mean  $\pm$  SEM). \* $p < 0.05$ , \*\* $p < 0.01$  Student's  $t$  test.



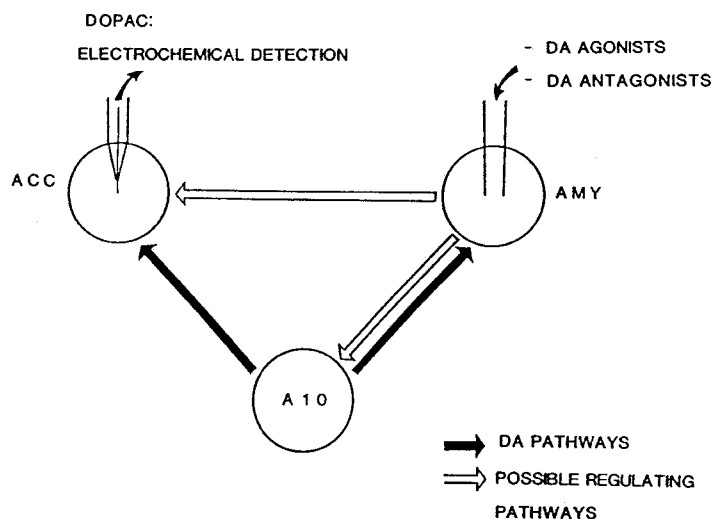
These results strongly support the hypothesis that the dopaminergic neurons have a modulatory influence on the structures they innervate rather than any specific intrinsic function. The partial restoration of normal behavior after treatment with L-DOPA (20) and after mesencephalic cell transplants (4, 28) also supports this view. These results have led to the suggestion (33) that dopaminergic neurons could be classified as regulatory neurons, as opposed to the integrative neurons situated in the projection areas. The integrative neurons can be grouped in different anatomofunctional systems (frontal system, limbic system, striato-limbic system).

The hypothesis proposed by Simon and Le Moal (33) suggested that the various dopaminergic pathways (e.g. mesocortical, meso-accumbens, meso-striatal) do not exert their regulatory action independently but have a coordinated functioning. This would facilitate information transfer from one integrating system to another.

#### FUNCTIONAL MODALITIES : INTERDEPENDENCE BETWEEN THE DIFFERENT PATHWAYS

We initially investigated functional interdependence between the dopaminergic projection of the nucleus accumbens and the amygdala by pharmacological manipulation of dopaminergic transmission in the amygdala, combined with measurement of dopaminergic activity in the nucleus accumbens (Fig.5). Changes in dopaminergic activity in the nucleus accumbens were studied using in vivo voltammetry, which enables continuous measurement of DOPAC, one of the metabolites of dopamine (11, 12, 24, 25). Dopaminergic transmission in the amygdala was manipulated by local injection of dopaminergic agonists or antagonists. Alteration of dopaminergic transmission in the amygdala was found to have significant effects on activity in the meso-accumbens pathway (Fig.6). The regulatory effect of the dopaminergic meso-amygdala projection on the meso-accumbens projection was found to be inhibitory, since stimulation in the amygdala by the dopamine agonist, amphetamine, reduced dopaminergic activity in the nucleus accumbens, and opposite effects were observed with dopamine antagonists.

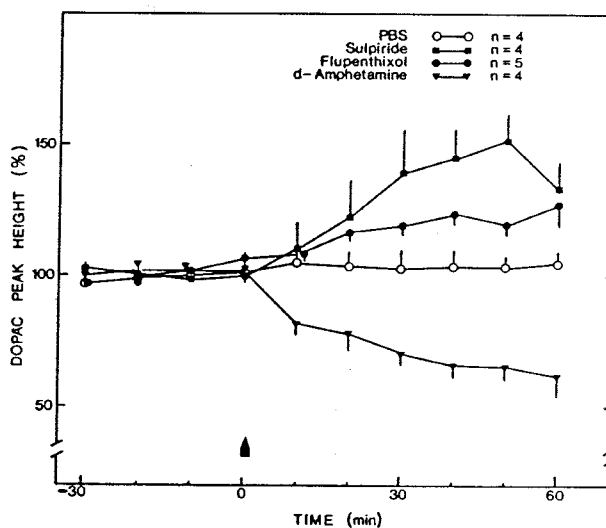
The functional interdependence could have behavioral consequences. We investigated this by measurement of the locomotor activity induced by injection of d-amphetamine, after specific 6-OHDA lesions of



*Figure 5 : Schematic diagram of the procedure used to investigate the functional interdependence between the dopaminergic projection of the amygdala and the nucleus accumbens. Alteration of dopaminergic transmission was achieved by local injection of dopaminergic agonists or antagonists in the amygdala. Dopaminergic activity in the nucleus accumbens was evaluated by the assay DOPAC levels. DOPAC was electrochemically detected in vivo using carbon fiber microelectrodes (DOPAC : 3,4-dihydroxyphenylacetic acid).*

the dopaminergic pathways in the amygdala. The amphetamine-induced locomotor response is regarded as a good index of dopaminergic activity in the nucleus accumbens (16).

After 6-OHDA lesions of the dopaminergic terminals in the amygdala, we observed increased locomotor activity in a circular corridor (Fig.7). Since local injection of dopaminergic antagonists in the amygdala increased dopaminergic activity in the nucleus accumbens, we supposed that 6-OHDA lesions of the amygdala increased dopamine turnover in the nucleus accumbens. The greater locomotor response to d-amphetamine of experimental animals could be due to increased



*Figure 6* : DOPAC peak height measured from voltammograms recorded from the nucleus accumbens after local injection of dopaminergic agonist (d-amphetamine), antagonists (sulpiride, flupenthixol) and solvent (PBS) in the amygdala. Results were expressed as the percentage (mean  $\pm$  SEM) of the respective mean pre-injection value. The arrow indicates the time of intracerebral injection (1  $\mu$ l/3 min). N represents the number of rats per group. Significant statistical difference observed between experimental and control groups (ANOVA) :  $F(1,6) = 23, P < 0.01$  (d-amphetamine/PBS),  $F(1,6) = 7.3, P < 0.05$  (sulpiride/PBS),  $F(1,7) = 5.6, P < 0.05$  (flupenthixol/PBS).

release of dopamine (with respect to controls), since release of newly synthesized dopamine is known to occur after amphetamine administration (22).

These results showed the existence of a functional balance between the dopaminergic pathways innervating the amygdala and the nucleus accumbens. It has been demonstrated that the mesocortical pathway regulates activity in the meso-accumbens and the meso-striatal dopaminergic pathways (1, 31). Moreover, current studies in this laboratory shown that enhanced activity of meso-accumbens pathway led to an increase in meso-striatal functioning. These considerations suggest that functional interdependence between these various pathways is a general characteristic of the mesencephalic dopaminergic system.

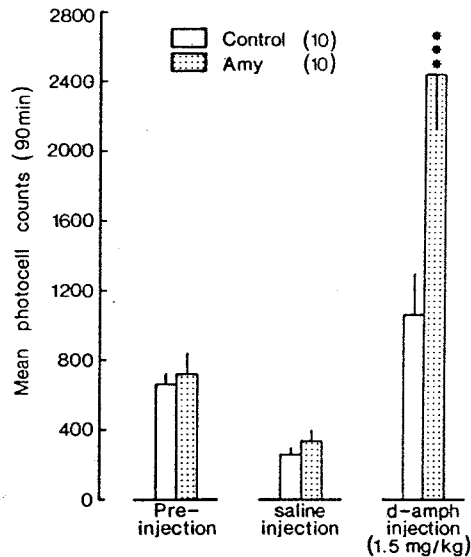


Figure 7 : Effect of 6-OHDA lesions of dopaminergic innervation of the amygdala on locomotor response to d-amphetamine in circular corridor test. D-amphetamine (1.5 mg/kg) injection was preceded by the habituation period and saline injection response (90 min each) (mean  $\pm$  SEM). \*\*\* $p < 0.001$  Student's  $t$  test.

#### CONCLUSION

It is suggested that dopaminergic neurons of the mesencephalon facilitate functions in the structures they innervate in a coordinated fashion. It is easy to envisage that such an integrating mechanism could contribute to behavior underlying environmental adaptation. When there is a change in the animal's environment, the following sequences of events could be set in motion : sensory afferents are stimulated, leading to stimulation of the ascending reticular system, which then directly or indirectly stimulates all dopaminergic pathways. This stimulation would facilitate information processing in the various structures innervated by the dopaminergic neurons. One of these integrating structures would be preferentially activated, depending on the exact nature of the task, while regulation of the other dopaminergic pathways would take place via pathways connecting the integrating structures and/or through

descending pathways going to the mesencephalon. These processes would thereby regulate the functioning of the integrating structures, especially the nucleus accumbens and striatum which have important connections with the motor system. These mechanisms would increase the probability of the behavioral response appropriate to the particular change in the environment.

Dysfunction in the pathways coordinating the different dopaminergic neurons may therefore lead to similar behavioral deficits as those due to dysfunction in the individual dopaminergic subunits themselves. This possibility may have implications for the etiology of certain psychiatric disorders.

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