MODULATION OF SELECTIVE PROCESSES IN LEARNING BY NEOCORTICAL AND LIMBIC DOPAMINE: STUDIES OF BEHAVIOURAL STRATEGIES

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INTRODUCTION

The main dopaminergic (DA) systems of the mammalian CNS are the diencephalic tubero-infundibular and incerto-hypothalamic (A11-14) and the mesencephalic long-axon (A8-10) projections to the forebrain (Lindvall and Björklund, 1978). The A9 group preferentially innervates the striatum and cingulate cortex (Beckstead et al., 1979), whereas the ventral tegmental area (VTA-A10) projects to the prefrontal, cingulate, suprarhinal and entorhinal cortices (mesocortical system, M/C) and underlying limbic structures such as the amygdala, septo-hippocampal complex and the nucleus accumbens (mesolimbic system, M/L, Simon, 1981).

Some of the major projection regions of the M/C and M/L systems show an extraordinary convergence of pathways from divergent sources (Phillipson, 1979). In discussing the integrative functions that this convergence implies we shall consider the prefrontal cortex and the septum (or N. accumbens) as representative of the M/C and M/L systems respectively (cf. fig.1).

Anatomical and electrophysiological studies show that the prefrontal cortex and septum are polysensory association areas (Mercer and Remley, 1979; Rosenkilde, 1979). Brain damage in both areas leads to impairments in learning and to changes in the "flexibility" of the early attention-related stages of information processing (Numan and Lubar, 1974; Brody and Pribram, 1978; Oades, 1979; 1982). Animals with prefrontal damage have difficulty with cross-modal integration (Petrides and Iversen, 1976), but the presentation of relevant cues ameliorates their impairment on delayed spatial or timing tasks (Crowne, 1983; Rosenkilde, 1979). After septal damage rats may learn abnormally fast (shock avoidance) or slow (appetitive operant/maze tasks). In some situations a relevant cue helps (classical/operant conditioning or maze learning: Burton and Toga, 1982; Donovick et al., 1979; Ellen et al., 1977); in others it does not help (spatial or avoidance tasks: Beatty and Carbone, 1980; Numan et al.,1982).

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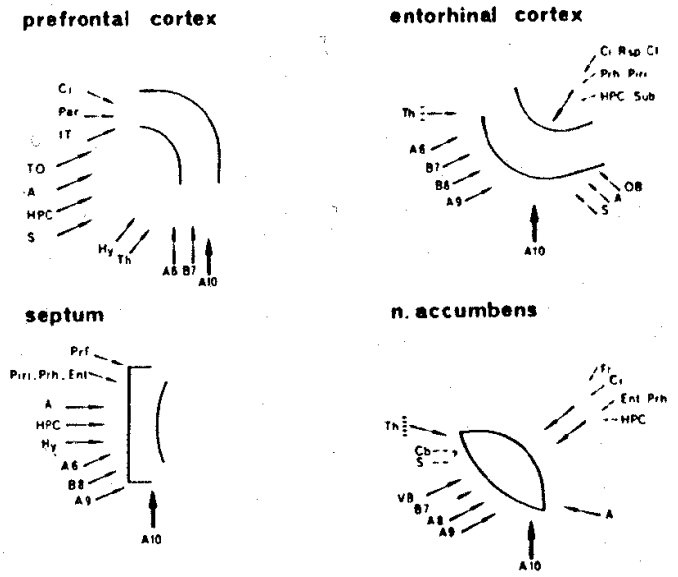

Fig.1. Convergence of afferents on M/C and M/L projection areas. A, Amygdala; Cb, Cerebellum; Ci, Cingulate cortex; Cl, Claustrum; Ent, Entorhinal cortex; Fr, Frontal cortex; HPC, Hippocampus; Hy, Hypothalamus; IT, Inferotemporal cortex; OB, Olfactory bulb; Par, Parietal cortex; Piri, Piriform cortex; PrF, Prefrontal cortex; Prh, Perirhinal cortex; S, Septum; Th, Thalamus; TO, Tuberculum olfactorium; A, B6-10, several monoaminergic nuclei.

DOPAMINE MODULATION

VTA-A10 lesions that deplete DA in the forebrain impair learning of a variety of complex appetitively and aversively reinforced tasks (Le Moal et al., 1977); but, as is usual after damage to complex association cortices, simple discriminations are not impaired (Simon, 1981). Yet appropriate levels of DA activity may not just be helpful but are probably crucial to adaptive learning. Extensive A9/A10 lesions can cause adipsia, aphagia, sensory neglect and abolish food-hoarding, pup-nursing, delayed alternation and active avoidance learning (see Oades, 1985).

In general terms DA may modulate the initiation and timing of responses and the switching of input-output relations in DA-innervated regions (Robbins and Everitt, 1982; Oades, 1985). But these accounts do not attempt to interpret the specific role of this modulation in the information processing particular to one or another brain area. The differences of learning performance found after non-specific electrolytic or specific 6-hydroxydopamine (6-OHDA) damage to DA projections illustrate the need for comparing M/C and M/L function. Thus delayed alternation is impaired after non-specific damage to the VTA, prefrontal cortex or septum (Simon, 1981; Markowitsch and Pritzel, 1976; Thomas,1979). It is also impaired after 6-OHDA damage to the VTA and prefrontal cortex (Simon, 1981; Brozovski et al., 1979). On active avoidance tasks electrolytic damage of the VTA produces a mild (Le Moal et al., 1969) or of the septum a strong facilitation (Numan et al., 1982), whereas prefrontal damage results in a mild deficit (Markowitsch and Pritzel, 1976). By contrast 6-OHDA lesions of the prefrontal cortex produce no effect and 6-OHDA lesions of the

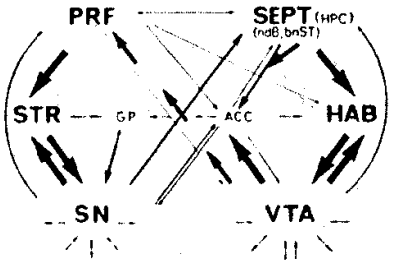

Fig.2. Frontostriate and septo(limbic)habenula axes with reference to M/C- and M/L-DA innervation from the substantia nigra (SN) and VTA. (Arrow size,- output importance as considered in text: note inclusion of closely linked limbic structures with septum (S) and integrative role of VTA shown by input/output arrows). ACC, N. Accumbens; HAB, Habenula; ndB, N. of diagonal band of Broca; PRF, Prefrontal cortex; STR, Neostriatum.

septum result in a mild facilitation of active avoidance, but 6-OHDA lesions of the VTA disrupt acquisition (cf fig.3).

STUDIES USING BEHAVIOURAL RECORDS

To improve our understanding of these region- and task-specific DA/non-DA interactions, one needs to know more than whether a given manipulation changes the latency or accuracy of performance on a task battery. One must ask how a stimulus can control or is hindered from controlling the output of a given region or system, for which behaviour is an indicator. When does a stimulus control? When is a response controlled? In the former case one finds out under what stimulus conditions an information processing channel is allocated (e.g. learned inattention). In the latter one records components of behavioural sequences as indicators of the control over information processing that allowed the particular output (e.g. task-solving strategy). In practice the two approaches overlap. A strategy of response is always required; the difference often lies with the number of response-determining events. The reasoning behind learned inattention has been elaborated elsewhere (Mackintosh, 1975). This discussion emphasizes the study of strategy (response sequences) that has only more recently attracted attention.

The importance of investigating behavioural strategies to the study of M/C and M/L function is illustrated by reference to the output of the prefrontal cortex and septum. The neostriatum receives a massive input from the frontal cortex (Beckstead,1979) and the septal (limbic) relations with the habenula and nucleus

accumbens are equally impressive (fig.2; Sutherland, 1982). Neostriatal activity seems to be important for gating sequences of behaviour appropriate to external (e.g.neighbours' behaviour) and to internal contingencies (e.g. own ongoing behaviour; Van den Bercken and Cools, 1982). Neostriatal treatment with DA antagonists or agonists can reduce or facilitate, respectively, the number of strategies rats may try in order to escape from drowning in a basin of water (Cools, 1980). Similarly damage to the habenula can drastically reduce the frequency of behavioural changes and the number of categories of behaviour (Thornton and Evans, 1982).

"Sequence-dependent Strategy"

We have been studying the efficiency of acquisition and the types of strategy used in a holeboard search task. In this task rats search a 16-hole arena for the 4 holes that always contain food. After 70-100 trials (10 trials/session, 2 sessions/day) rats learn to avoid empty holes and to visit food holes in a preferred order (strategy) that differs between individuals (Oades and Isaacson, 1978; Oades, 1981a; 1982).

In a recent experiment animals received the neuroleptic spiroperidol (2 µg/0.5 µl), apomorphine (DA agonist) or vehicle (pH adjusted tartarate solution) directly into the VTA 15 min before sessions 4 and 7 (Oades, 1981c). Although a degree of diffusion was expected after this treatment, the neurochemical and behavioural sequelae of injection sites 1.5 mm outside the VTA were quite different. Neuroleptic but not other treatments increased rearing (3-4 fold), the number of errors (50-100%) and the number of switches away from the preferred strategy (Oades, 1981c). Some animals were sacrificed after session 7. After neuroleptic treatment there was an increase of DA utilization in the N. accumbens (table 1). This increase correlated with increased rearing (N, 18; $r=0.52$; $p<0.05$; Spearman rank correlation) and with the number of errors ($r=0.52$; $p<0.05$). The correlation was similar whether the errors were classified according to working or reference memory. But there was no significant correlation with the number of strategy repetitions or changes ($r=0.2$).

In view of the hippocampal input to the habenula and N.accumbens it is interesting that an earlier report showed that hippocampal damage resulted in animals making more errors and frequent changes of strategy. After haloperidol treatment (ip) such animals made fewer errors but continued to change their strategy (Oades and Isaacson, 1978). Thus it is possible that whereas the M/L system may be involved in an error evaluation process (necessary for a succesful strategy), an important contribution to the sequential organization of appropriate responses may arise elsewhere. The work of Cools and our own report that haloperidol alone can disrupt strategy development suggests that the fronto-striate axis may be important. Whereas haloperidol treatment reduced the number of strategy repetitions (quantity), cortical damage increased the range of hole-visit sequences attempted (quality)(Oades and Isaacson, 1978). Damage was more temporo-parietal than frontal, but the possibility of an interaction at the level of the prefrontal cortex was supported by the results of treating cortically-damaged animals with a neuroleptic. Working but not reference memory types of error (ie intra-trial) showed a slight improvement (Oades, 1981b). A differential impairment for working/episodic rather than for

Table 1. Levels (pmol/mg wet weight) and ratios of monoamines and metabolites in N. Accumbens (±SEM)

Group	DA	DOPAC	DOPAC/DA	NA	5HIAA/5HT
C	38.8 ±6.2(7)	7.4 ±2.1(6)	0.19 ±0.04(6)	4.74 ±1.14(5)	0.29 ±0.01(7)
SP	64.1 ±2.6(5)	18.6 ±1.5(5)	0.30§§ ±0.03(5)	4.6 (1)	0.34 ±0.03(5)
AP	23.0 ±3.1(4)	4.3 ±1.4(3)	0.18 ±0.03(3)	3.0 ±0.43(3)	0.47 ±0.17(4)

Reverse phase HPLC analysis, electrochemical detection (0.8 v)(0.1M citrate-phosphate buffer, pH 3.5, 0.1 mM EDTA, 0.4 mM sodium octylsulphate, 15% (v/v) methanol (Rea et al., 1982). C, control; SP, spiroperidol- and AP. apomorphine-treated rats (in VTA): n, number of samples: §§ $p<0.02$ Student's T test.

reference/semantic memory tasks has also been noted for Parkinsonian patients (Weingartner et al., 1984).

The implication is that frontal areas may be involved in strategy formation and the prefrontal-DA component is active in determining the adaptive quantity of a particular strategy. This is not entirely unexpected. Monkeys with frontal damage are slow to acquire a 3-key press contingent discrimination (Brody and Pribram, 1978) and frontally damaged rats are poor at relearning a rod-lever press sequence (Mogenson and Divac, 1984). Human subjects with frontal damage have difficulty in using experimenter-provided negative feedback in directing the future sequence of discrimination choices between stimuli varying on 4 binary dimensions (i.e. impaired development of an adaptive lose-shift strategy, Cicerone et al., 1983). Further definition of the role of prefrontal DA could be achieved by manipulation of the number, salience and relevance of cues available to determine the strategies chosen and to solve the tasks chosen (cf next section).

"Event-dependent Strategy"

We have started to study stimulus control in a two-way active avoidance task. The rate of learning of normal rats improved slightly after adding a light to a tone stimulus (simple/compound CS). This was clearly so for prefrontal- but not for septal-6-OHDA-treated animals (fig.3). (This recalls effects of cues on task performance after electrolytic damage; see introduction).

Animals treated with 6-OHDA in the septum were moved onto a conditioned blocking test. (Avoidance responses to separately presented non-reinforced tone and light stimuli shown by animals with shocked tone and light (ab) experience for two sessions were compared to those from animals pre-exposed to one of the stimuli on the first session (a/ab)). The conditioned avoidance blocking ratio (b/a+b) over 20 presentations of the stimuli alone for the septal-6-OHDA group was a satisfactory control value of 0.18(i.e. animals did not learn well the association between "b" and the shock). This is opposite to expectations from previous results obtained for animals with electrolytic damage of the septum

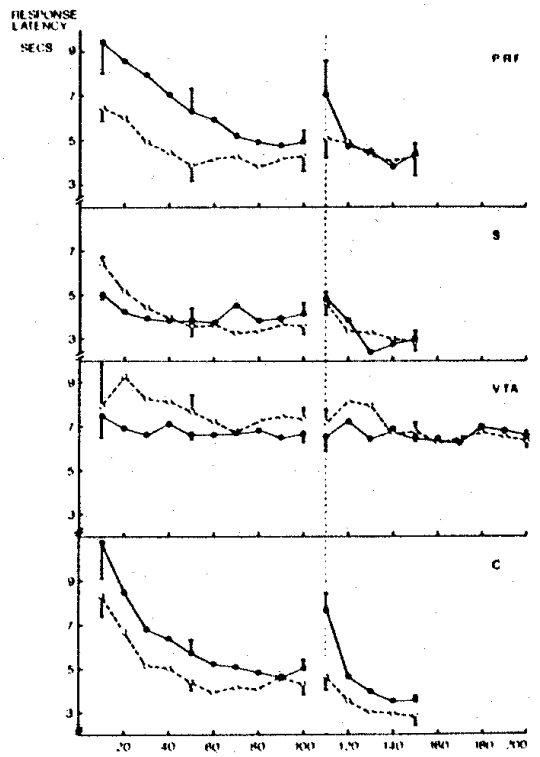

Fig.3. Latency (SEM) to avoid footshock in a shuttle box over two 100 trial sessions is shown for 4 groups: ascorbic acid (C;n,18) or 6-OHDA (4 ug/ul/side + 20 mg/kg DMI) in A10 (VTA; n,10), septum (S; n,11) or prefrontal cortex (PRF; n,13). A tone (1 KHz, 85 dB: white noise 65 dB) (——) or a tone with light (100 Lux)(---) were presented 5 sec before shock (1 mA). Training stopped after acquisition (80% on 3 successive 10 trial blocks). The VTA group did not learn to avoid: the two vs one stimulus condition facilitated acquisition for the prefrontal and control but not for the septal group (Analysis of variance, H 14.8; df 2, $p<0.001$, Kruskal Wallis).

(Weiss et al., 1974). But a closer look at the response latencies to the first and last three stimuli shows this to be an over simplified conclusion (fig.4). At first, blocking was attenuated. Finally the septal group showed better blocking than the controls. Overall the demonstration of blocking in the animals treated with 6-OHDA in the septum confirms the hypothesis of Solomon whereby an attenuation of blocking results from DA hyperactivity (Crider et al., 1982; Solomon et al., 1981). But taken trial by trial we found a "change-over" of responsiveness.

A potentially similar "change-over" from responding to non-responding depending on stimulus exposure has also been reported on a latent inhibition task. Burton and Toga (1982) pre-exposed animals to non-reinforced presentations of the to-be-discriminated stimulus. Rats with largely unilateral electrolytic damage to the septum showed an attenuation of latent inhibition after many exposures (180+) but an enhancement after fewer pre-exposures (<100). They suggested that there may have been a change of

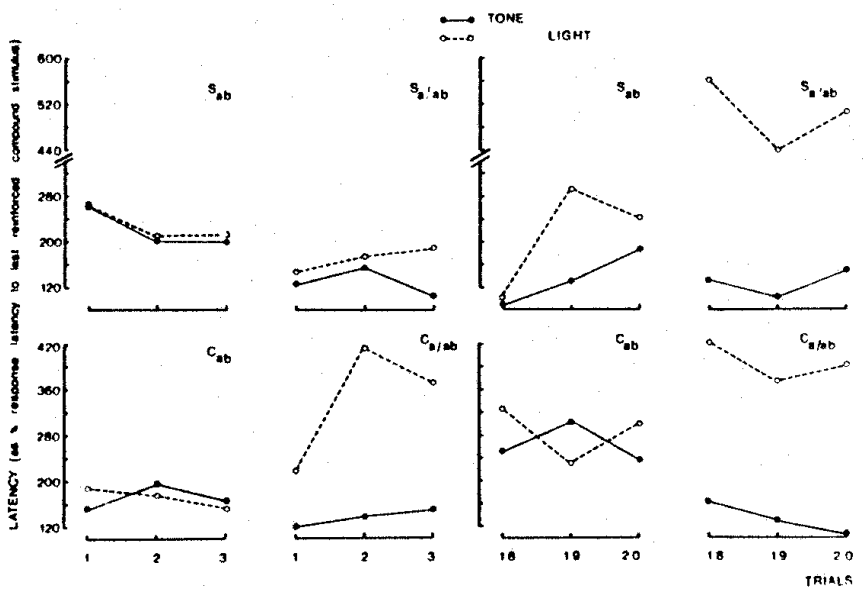

Fig.4. Response latencies to the first (left) and last (right) three presentations of a non-reinforced tone (a:——) or light (b:---) in a shuttle box after avoidance training with "ab" or "a" followed by "ab". Latencies are shown as a percentage of that for the last reinforced presentation of "ab". (Test program: a,b,a,ab,b,a,b,ab, etc). Animals received 6-OHDA (S; n,11) or vehicle (C; n,18) in the septum. Blocking to "b" followed attenuation in the S a/ab group (X^2_r 11.6, $p<0.05$, Friedman two way analysis of variance).

sensitivity or a sensitization effect. Although animals with electrolytic septal lesions are reported to be more sensitive to shock and light (Clody and Carlton, 1969; Chafetz et al., 1981), we have not found animals with 6-OHDA lesions of the septum to be especially sensitive to footshock or tone (in prep). We also looked at the latency to enter a dark then to return to a strongly lit (100 W) compartment of a two-chamber box (Bruneau et al., 1980). After septal-6-OHDA treatment rats entered the dark compartment with a latency comparable to controls (mean, S, 11.8; C, 18.4 sec) but they returned to the light chamber later (104 vs 52 sec; $p<0.05$ Mann Whitney U test). A similar result was found after 6-OHDA treatment of the N. accumbens (Taghzouti, 1983). But 9 of the septal animals in fact poked their noses back into the light chamber long before they emerged (38 vs 141 sec). The remaining septal animals were comparable to controls in that they usually emerged after poking their noses out into the light chamber.

Another example of an apparent "change-over" of responsiveness was found in the sequences of unrewarded visits shown by rats exploring the three arms of a Y-maze (cf Oades et al.,1985). Overall both lesioned (septal-6-OHDA) and control animals showed a strategy for visiting the least-recently visited arm (choice alternation; 61-70%). But whereas a control animal revisited the most-recently visited arm (perseverative choice) once in the

in the first 8-12 choices, a lesioned animal made 3-4 changes of choice strategy in this time. Yet after 25-30 choices lesioned animals showed perseverative choices less often than controls (i.e. fewer strategy changes). In assessing this result it is important to note that opposite results have been reported with different techniques and animals. Improved alternation, spatial discrimination and reversal performance were reported after septal-6-OHDA damage in mice (Galey et al., 1984), but small amounts of electrolytic septal damage in rats resulted in performance deficits (Thomas, 1979).

The DA-A10 input to the septum exerts a tonic inhibition and 6-OHDA damage to the septum a disinhibitory effect on cholinergic activity in the septo-hippocampal pathway (Durkin et al., 1983; Galey et al., 1984). This lesion may decouple the coordination of information processing controlled by septo-hippocampal input from the temporal pattern of environmental factors that inform on the appropriateness of the response and ultimately the need for a change of strategy. What might these factors be? In normal rats the nature of the reinforcement schedule and the degree of exposure to the stimuli (exploration) determine the tendency to repeat or to shift response choice (Evenden and Robbins, 1984; Haig et al., 1983). Since the suppression of responding by animals with electrolytic septal damage on schedules requiring differential responding (DRL) is reported not to be solely determined by the density and distribution of reinforcement (Ellen et al., 1978), we would emphasize the important role of stimulus exposure and timing factors. In animals with 6-OHDA-septal damage the influence of important strategy determining information is displaced, not absolutely, but temporally. This "decoupling" of septo-hippocampal processing from an input that inhibits processing (i.e.disinhibition) leads at the behavioural level to a change of responsiveness temporally inappropriate to the environmental circumstance.

CONCLUSIONS

DA activity in both M/C and M/L systems is crucially involved in adaptive learning. Studies of behavioural strategies in simple-event and complex-task situations both contribute to elucidating the interdependence of these systems in organizing appropriate response sequences (nature and quantity: frontostriatal and septo(limbic)habenula axes). The M/L system appears important for the evaluation and temporal coordination of response feedback and the M/C system for the integration of succesful responses in to appropriate strategies. Both processes are dependent on timing and on input/output switching that are attributable to DA activity (Oades, 1985; Robbins and Everitt, 1982). Speculative as these working hypotheses are, they encourage further development of a combined psychological, ethological and neurobiological approach to the investigation of the M/C and M/L systems for which this report represents but an early stage.

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