The Neurobiological Substrates of Depression in Parkinson's Disease: A Hypothesis

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ABSTRACT: Evidence from a variety of sources indicates that the mesolimbic-mesocortical dopamine projections may play an important role in some types of reward or reinforcement processes in animals. There is circumstantial evidence that this is also true in humans. Since a reduced ability to experience pleasure or reward (i.e. anhedonia) is a cardinal feature of clinical depression, and since the mesolimbic and mesocortical dopamine projections have been shown to degenerate in Parkinson's disease, it is suggested that damage to these reward-related systems may contribute directly to the high incidence of depression that has been reported in this disease.

RÉSUMÉ: Plusieurs arguments indiquent que les projections dopaminergiques mésolimbiques-mésocorticales, jouent un rôle important dans certains processus de récompense ou de renforcissement chez l'animal, et peut être chez l'humain. Puisqu'une habilité réduite à ressentir un plaisir ou une récompense (anhédonie) est une composante importante de la dépression clinique, et puisque les voies dopaminergiques mésolimbiques et mésocorticales peuvent dégénérer dans la maladie de Parkinson, nous suggérons que ces systèms de récompense jouent un rôle dans le taux élevé de dépression rapporté dans cette maladie.

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In his classic essay Parkinson (1817) recognized that depression is often observed in the disease that has been named after him. Since that time, depression associated with Parkinson's disease has been demonstrated repeatedly by a variety of clinical researchers (Warburton, 1967; Mindham, 1970; Brown and Wilson, 1972; Celesia and Wanamaker, 1972; Horn, 1974; Mindham et al., 1976; Robins, 1976; Mayeux et al., 1981). Whether this depression is of a reactive or endogenous nature is not presently certain. For example, depression as a reaction to a progressive, debilitating neurological disorder is thought by some to be sufficient basis for the high incidence that is observed in Parkinson's disease. On the other hand, the incidence of depression in other serious chronic diseases appears to be substantially less than that observed in Parkinson's disease, and this has led to the suggestion that depression in Parkinson's disease is not simply of the reactive type but may, in many instances, be directly associated with the pathobiology of the disease itself. Recent developments in research concerning the neurobiological substrates of reward in experimental animals have provided some interesting support for the latter suggestion. On the basis of these studies the following hypothesis may be advanced: depression in Parkinson's disease is associated with degeneration of the mesolimbic and/or mesocortical dopamine systems. Some research findings that are relevant to this hypothesis are reviewed briefly below.

One of the most difficult problems in studying the neurobiological substrates of endogenous depression is the absence of acceptable animal models of this syndrome. We have chosen a different strategy in addressing this problem by attempting to identify systems in the brain that mediate reward or reinforcement processes. The rationale for this approach is that anhedonia or a lack of ability to experience reward or pleasure is considered a cardinal feature of clinical depression. This raises the possibility that the function of certain reward-related neural systems is impaired in depression. Recent research concerned with the neurobiological substrates of reward suggests that the mesolimbic and/or mesocortical dopamine projections appear to be reward-related systems in the brain. The first direct evidence for a role of these projections in reinforcement was obtained by Phillips and Fibiger (1978) who implanted electrodes in the A10 region of the ventromedial tegmentum of the rat, the origin of the mesolimbic-mesocortical dopamine projections. When given the opportunity, these rats learned to barpress at very high rates for electrical stimulation at these electrode sites. By itself, this does not prove that intracranial self-stimulation (ICSS) of the dopamine-containing neurons in the A10 region is reinforcing because many other, non-dopaminergic systems in the vicinity of the electrodes would also be activated by the electrical stimulation. However, the next phase in these experiments did provide considerable support for the involvement of the dopamine-containing neurons. Specifically, when the ascending projections of the dopamine-containing neurons were lesioned by the selective neurotoxin, 6-hydroxydopamine (6-OHDA), self-stimulation was greatly reduced in the animals with electrodes in the A10 region. Control experiments indicated that this was not due to a lesion-induced motor impairment that interfered with the ability of the animal to perform the barpass response. It should be pointed out that similar experiments on ICSS obtained from electrodes in the zona compacta of the substantia nigra (A9) have indicated that dopamine-containing neurons do not mediate the reinforcing effects of ICSS in the substantia nigra (Clavier and Fibiger, 1977). Therefore, in contrast to the projections arising from the A10 region, the nigro-striatal dopamine projection does not appear to be a reinforcement related system. It is unlikely, therefore, that its degeneration is directly responsible for the depressive symptoms in Parkinson's disease.

Other paradigms have also been used to evaluate the role of the mesolimbic-mesocortical dopamine system in reinforcement.

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One of these is intravenous self-administration of sympathomimetic drugs such as cocaine and amphetamine. These compounds are known to increase the release and/or block the re-uptake of catecholamines. There is considerable pharmacological evidence that the reinforcing effects of these compounds are mediated by dopaminergic mechanisms (Yokel and Wise, 1976; Roberts et al., 1977). Noradrenergic systems do not appear to be important (Roberts et al., 1977). A number of studies have implicated dopamine-containing terminals in the nucleus accumbens as being critical for the reinforcing effects of cocaine and d-amphetamine. Perhaps the clearest evidence of this was the demonstration by Roberts et al. (1980) that extensive 6-OHDA induced lesions of dopamine-containing terminals in the nucleus accumbens caused rats that had previously been trained to self-administer cocaine to cease responding after the lesion. This was not due to some motoric impairment produced by the lesion because high rates of bar-pressing were observed on the first day after the lesion that the animal was given access to the cocaine. The pattern of responding on this day was reminiscent of that typically observed during extinction, such as when saline is substituted for the cocaine solution. This pattern consisted of high rates of responding during the early part of the experimental session followed by a gradual slowing and eventual cessation of responding by the end of the session. The clear implication of these results is that 6-OHDA lesions of the nucleus accumbens blocked the reinforcing properties of intravenous cocaine. Lyness et al. (1980) have conducted related experiments with d-amphetamine, showing that rats with these lesions fail to initiate self-administration despite nearly three weeks of post-lesion testing. In addition, animals already trained to self-administer d-amphetamine ceased responding for intravenous injections of the drug after 6-OHDA lesions of the nucleus accumbens.

Although these studies implicate dopamine-containing terminals in the nucleus accumbens in the reinforcing properties of cocaine and d-amphetamine, a recent study by Goeders and Smith (1983) indicates that consideration should also be given to dopamine-containing terminals in the medial prefrontal cortex. These investigators demonstrated that rats will self-administer cocaine directly into this part of the brain. Because 6-OHDA lesions of the nucleus accumbens may damage dopamine-containing fibers of passage that innervate the medial prefrontal cortex, it remains possible that the effects of 6-OHDA injections into the nucleus accumbens on intravenous self-administration of psychostimulant drugs is due to a dopamine deficiency in the medial prefrontal cortex rather than in the nucleus accumbens. This possibility is currently being investigated. In any event, these experiments on intravenous self-administration provide strong support for the hypothesis that the mesolimbic and/or mesocortical projections are important reinforcement related systems.

The third line of investigation that has been used to investigate the role of dopamine-containing systems in reward is place preference conditioning. In this paradigm, animals are exposed repeatedly to two distinct environments; one of these is always paired with an injection of a drug such as cocaine or d-amphetamine, the other with an injection of the vehicle. Subsequently, when the animals are given a choice of spending time in either of the two environments it has been found that they prefer the drug-associated side. Recently, Spyraki et al. (1982a) demonstrated that the dopamine receptor antagonist haloperidol could prevent the place preference conditioning that is normally produced by d-amphetamine. It was also found that 6-OHDA lesions of the nucleus accumbens influenced d-amphetamine induced place preference conditioning in such a manner that the amount of dopamine remaining in the nucleus accumbens correlated significantly with the degree of place preference conditioning. In similar experiments with cocaine, neither dopamine receptor antagonists nor 6-OHDA lesions of the dopamine-containing neurons were found to prevent the place preference conditioning that is produced by this drug (Spyraki et al., 1982b). This suggests that the reinforcing properties of cocaine cannot be attributed entirely to effects on central dopamine-containing systems and that other factors must also contribute. It is interesting to note in this regard that procaine, a drug that shares cocaine's local anaesthetic properties but which does not block dopamine uptake, also produced place preference conditioning (Spyraki et al., 1982b). This suggests that the mesolimbic-mesocortical dopamine system is but one of what are probably multiple reinforcement related systems in the brain.

In addition to the data obtained from experimental animals, evidence from human studies is consistent with the view that central dopamine-containing systems mediate certain aspects of reward or reinforcement. For example, pretreatment with α-methyl-para-tyrosine (AMPT), which blocks the synthesis of catecholamines, causes human subjects to give decreased ratings of the euphoric effects of intravenous amphetamine (Jonsson et al., 1971). Because AMPT reduces the synthesis of both dopamine and nonadrenaline, this study could not discriminate between a dopaminergic and noradrenergic mediation of this effect of amphetamine. In a subsequent study, however, Gunn et al. (1972) reported that pretreatment with the specific dopamine receptor blocker pimozide reduced amphetamine-induced euphoria in human subjects. The noradrenergic receptor antagonists phenoxybenzamine and propranolol were not effective in this respect.

As is evident above, there is now a considerable body of experimental evidence indicating that the mesolimbic and/or mesocortical dopamine projections mediate some aspects of reward or reinforcement. Degeneration of these systems in Parkinson's disease might well, therefore, be expected to result in a reduced capacity to experience reward or pleasure, this state of anhedonia being an important feature of depressive illness. The question arises as to whether there is significant damage to the mesolimbic-mesocortical dopamine system in Parkinson's disease. In this regard it is interesting to note that it has been known for some time that in addition to the well documented degeneration of the nigro-striatal dopamine system in Parkinson's disease, limbic regions also show decreases in chemical markers for dopamine-containing neurons (McGeer and McGeer, 1976; Price et al., 1979). More specifically, Javoy-Agid et al. (1981) have shown that the activity of tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, is reduced in both the substantia nigra and ventral tegmental area of patients dying with Parkinson's disease. According to these authors, the decrease in enzyme activity was less severe in the ventral tegmental area than in the substantia nigra. The failure to observe equivalent decreases in these areas may have interesting clinical and therapeutic implications. For example, although depression is a common feature of Parkinson's disease, it is not observed universally in these patients. According to the hypothesis proposed here, depression would be seen in those patients in whom the degeneration of the mesolimbic-mesocortical dopamine system is most severe. The observations of Javoy-

Agid et al. (1981) may also explain the wide variability that has been reported concerning the antidepressant efficacy of l-dopa in Parkinson's disease. For example, although l-dopa has been claimed to have antidepressant effects in Parkinson's disease (Celesia and Wanamaker, 1972; Yahr et al., 1969), others have reported that it is ineffective or even deleterious in this respect (Mindham et al., 1976; Barbeau, 1969). If the degeneration of the mesolimbic-mesocortical systems is not always equivalent to that of the nigro-striatal projection in Parkinson's disease, then doses of l-dopa that are effective in treating the motor symptoms resulting from nigro-striatal damage, may not be appropriate or suitable for restoring normal function to the other dopamine-containing systems. Another factor that may contribute to the equivocal utility of l-dopa in treating depression associated with Parkinson's disease is that cholecystokinin (CCK) has been shown to co-exist with dopamine in the mesolimbic system (Hokfelt et al., 1980 a, b). Therefore, by itself l-dopa may not be sufficient to treat the symptoms resulting from damage to this system. Presumably, postsynaptic neurons in limbic regions require both dopamine and CCK to be activated or inhibited normally by the presynaptic terminals of the mesolimbic projection. This raises the possibility that co-administration of l-dopa and CCK or its analogues might be more effective in the treatment of depression in Parkinson's disease.

Although the present discussion has emphasized the possible role of the mesolimbic and/or mesocortical dopamine projections in depression in Parkinson's disease, a possible contribution of noradrenergic, and in particular, serotonergic systems cannot be ruled out at this point. There is evidence that both noradrenergic and serotonergic neurons are damaged in Parkinson's disease (Sourkes, 1976; Riederer et al., 1977). A role of the noradrenergic system that arises in the locus coeruleus seems unlikely for a number of reasons. First, this is not a reinforcement or reward related system (Fibiger, 1978; Wise, 1978). Second, to the extent that noradrenergic mechanisms are involved in the therapeutic efficacy of tricyclic antidepressants, this appears to be due to a down-regulation of central noradrenergic synapses rather than an up-regulation as originally proposed (Sulser, 1978; Bergstrom and Keller, 1979; Huang et al., 1980). Presently, the contribution of serotonergic mechanisms in depression in Parkinson's disease is more difficult to evaluate because of the relative lack of data concerning the role of serotonergic systems in normal and abnormal behaviour.

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