The nature of central dopamine receptor supersensitivity

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Receptors within the peripheral nervous system develop the phenomenon of supersensitivity if they are deprived of their natural chemical transmitter for any length of time (Thesleff, 1960; Trendelenburg, 1966). The same principle has been applied to the central nervous system, and, for example, has been suggested to explain the changes observed in animal behaviour following manipulation of the central dopaminergic mechanisms. The pharmacological basis of the rotating rodent is an important application of this principle, where degeneration of one nigro-neostriatal dopaminergic pathway is believed to be associated with the production of supersensitive striatal dopamine receptors. This phenomenon results in an animal that circles away from the side of the lesion when systemically administered directly-acting dopamine agonists, due, it is suggested, to a preferential stimulation of these supersensitive receptors (Ungerstedt, 1971).

In the periphery, 're-innervation' of the denervated receptor is associated with a return of receptor function towards normal (Thesleff, 1960). Since complete functional re-innervation is not possible within the central nervous system, little is known of the nature of the dopamine receptor rendered supersensitive by presynaptic degeneration. However, a partial 're-innervation' of these central receptor sites can be achieved by the chronic oral administration of levodopa (L-DOPA), the direct precursor of dopamine. Such would be its effect in the L-DOPA therapy of Parkinson's disease.

The turning mouse model of von Voigtlander & Moore (1973) was used as a test of the function of supersensitive striatal dopamine receptors. Dose-circling response curves to systemically administered L-DOPA (range 10–200 mg/kg, plus the peripheral decarboxylase inhibitor, carbidopa, 25 mg/kg) were conducted in two groups of mice with unilateral 6-hydroxydopamine induced destruction of striatal dopaminergic nerve terminals. One of these groups was fed L-DOPA chronically in the diet.

Although chronic oral administration of L-DOPA for two months increased spontaneous locomotor activity and induced spontaneous contraversive circling behaviour, it did not significantly alter the circling response induced by systemically administered L-DOPA. Similarly, withdrawal of L-DOPA from the diet did not influence L-DOPA induced circling behaviour, although both spontaneous locomotor activity and spontaneous turning behaviour returned to control levels. Biochemically, chronic administration of L-DOPA to a further group of mice caused only modest (25–30%) increases in cerebral dopamine concentrations on both the lesioned and intact sides; noradrenaline and 5-hydroxytryptamine levels were unaltered.

The behavioural results suggest that central dopaminergic denervation 'supersensitivity' is permanent in nature. However, as in Parkinson's disease, administration of L-DOPA to this animal model did not restore the dopamine concentrations on the side of the lesion to normal. Thus functional re-innervation may have been only partial, and the possibility that complete functional re-innervation could reverse dopamine receptor supersensitivity cannot be dismissed.

These somewhat unexpected results may convey a warning. Perhaps it is not strictly correct to compare animal models, where apparent supersensitivity is developed very rapidly following an acute lesion, with human neurological disorders such as Parkinson's disease, where the condition may take months or years to achieve complete functional loss of presynaptic terminals.

References

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