On the presence of dopamine in the mammalian spinal cord

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McGeer & McGeer (1962) reported that dopamine (DA) was present in the spinal cord of several mammalian species in a concentration range of 0.20-1.00 μg/g. The results were not subsequently verified (Andén, 1965; Anton & Sayre, 1964; Laverty & Sharman, 1965) and most authors accept that DA is not present in the mammalian spinal cord.

In the course of work designed to study the effects of monoamines (MA) on the stretch reflex in the decerebrate rat (Commissiong & Sedgwick, 1973, 1974), it was necessary to verify the absence of DA from the spinal cord. We have, however, consistently found a substance in the cord having identical fluorescence characteristics with DA and with putative DA from the forebrain and brainstem, Figure 1. A modified procedure of the fluorimetric method of Fleming, Clark, Fenster & Towne (1965) was used to assay DA.

The concentration of DA found in the cord in μg/g ± s.d. was 0.13 ± 0.07 (n = 11), compared with 0.19 ± 0.05 (n = 13) for the brainstem and 0.94 ± 0.16 (n = 2) for the forebrain.

The substantia nigra is the origin of most of the known central dopaminergic pathways but a direct nigrospinal tract is not known to exist (Ungerstedt, 1971). This conclusion, however, is based primarily on results obtained from the histochemical fluorescent technique, which distinguishes between DA and noradrenaline (NA) only indirectly, after prior pharmacological manipulations (Dahlstrom, 1969).

Our results indicate that dopamine is present in the spinal cord of rat, in a concentration high enough to preclude the possibility that it is acting simply as a precursor for NA. If this is so, the likelihood exists that DA is a spinal transmitter. This means that the currently accepted interpretations of the effects of L-DOPA on spinal mechanisms might be in need of reinterpretation.

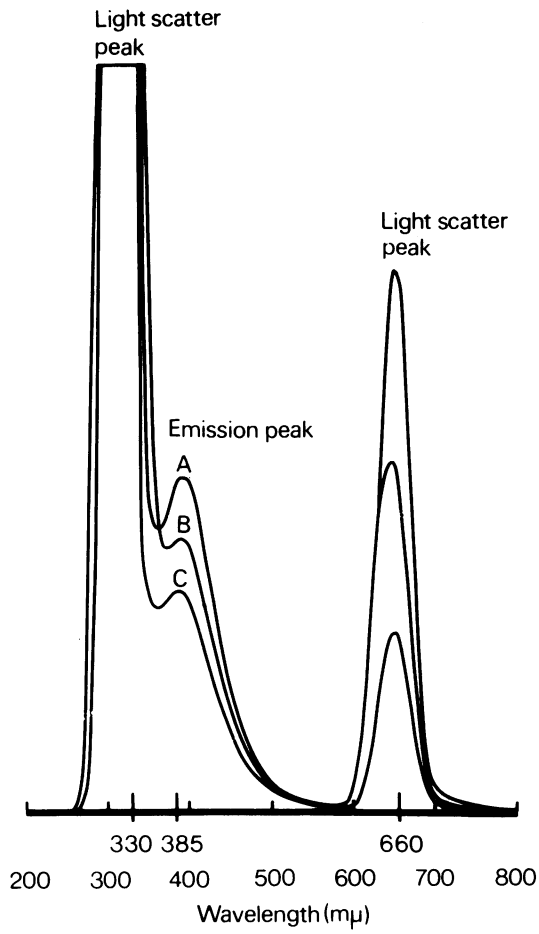

Fig. 1 Emission spectra of the putative DA fluorophore from the forebrain (A), brainstem (B) and spinal cord (C) of the rat. Excitation and emission peaks (330 mμ and 385 mμ respectively) for each, were identical with those for DA. Each trace is of two superimposed scans.

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Lethal plasma concentrations of pralidoxime methane sulphonate (P2S) given parenterally

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Pralidoxime methane sulphonate (P2S), given by i.m. or i.v. injection, is standard therapy for oxime-sensitive organophosphorus poisoning. Plasma concentrations of at least 4 μg/ml are required for optimum therapeutic effects (Sundwall, 1961), and can be achieved in man within 5 min of receiving 500 mg i.m. (Holland, Parkes & Shakespeare, 1972). In the rabbit we found the acute LD_{50} of P2S to be 258 mg/kg i.m. and 118 mg/kg i.v. Others quote 356 mg/kg i.m. for monkeys, 145 mg/kg i.v. for rabbits (Davis & Willey, 1958), and 125 mg/kg i.p. for mice (Barkman, Edgren & Sundwall, 1963). The variation between these values, and the necessity to determine the ratio of therapeutically effective to toxic plasma concentrations, lead us to investigate what constitutes a lethal plasma level of the drug.

Plasma P2S concentrations were measured (Creasey & Green, 1959) sequentially in female rabbits for up to 2 h after receiving the LD_{50} of P2S by i.m. (258 mg/kg) or i.v. (118 mg/kg) injection.

Typical results are shown in Figure 1. Following the i.m. LD_{50} there may occur: (a) a progressive rise in plasma concentration with early death at levels >200 μg/ml; (b) a rapid rise to 100-150 μg/ml which is maintained for 30-40 min, then an abrupt increase with death at concentrations >200 μg/ml; (c) a rise to peak concentrations <100 μg/ml followed by a slow decline with survival. After the acute i.v. LD_{50} there occurs either a rapid rise in concentration with death at levels >200 μg/ml, or an increase to 100-200 μg/ml and then a prompt and continuous fall with survival.

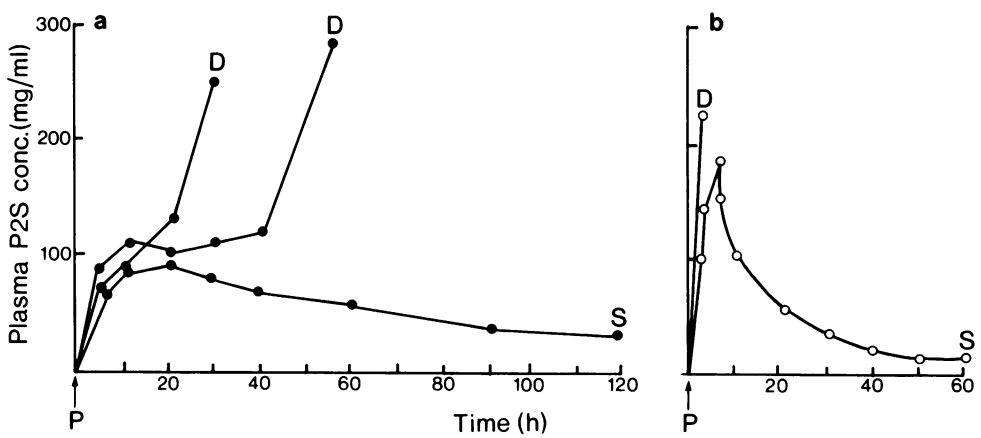

Fig. 1 Typical changes in plasma P2S concentrations in rabbits that survived (S) or died (D) following an injection (P) of the acute i.m. LD_{50} (●) or i.v. LD_{50} (○) of P2S.

The results suggest:

(a) Plasma P2S concentrations at death are >200 μg/ml;