LETTERS TO THE EDITOR

Tremor induced by *S*-adenosyl-L-methionine: possible relation to L-dopa effects

CLIVE G. CHARLTON, E. LEONG WAY, *Department of Pharmacology, University of California, San Francisco, California*, 94143, *U.S.A.*

S-Adenosyl-L-methionine (SAM) is a native substance found in the body including the brain. Its role is significant in that it participates in terminating the activity of biogenic amines at nerve endings. SAM is the methyl donor for the extraneural metabolism of catecholamines (Axelrod, 1971), and may be involved also in their reuptake (Eisenfeld, Axelrod & Krakoff, 1967). Since the metabolism of SAM can be manipulated experimentally, it would appear that such manoeuvers could have profound effects on central nervous function. It appeared worthwhile to examine the behavioural effects of SAM in the intact animal. To our surprise a search of the literature revealed no description of the pharmacological profile of the compound.

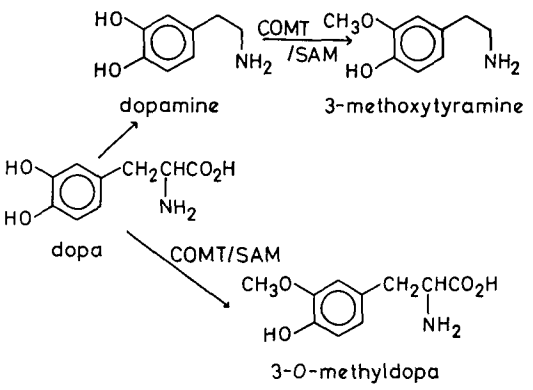
It was observed that SAM when injected intracerebroventricularly (i.c.v.) caused marked impairment of motor function in ICR mice. The dominant effect is tremor and with increasing dose, vigorous body shaking occurs. Impaired posture, spontaneous jumping, apparent poverty of movement and episodes of convulsion are also seen. There are two components to the tremor that are easily demonstrable: (1) postural tremor and shaking and (2) rapid intermittent quivering body movements when the mouse is suspended by the tail. The latter response is detectable by lower doses and is of a longer duration than the postural tremor.

The onset, intensity and duration of the SAM effects are dose-dependent. Doses were given in 5·0 μl of 0·9% w/v NaCl. A dose of 4×10^{-7} mol per mouse (7·18 mg kg^{-1}, i.c.v.) or greater caused tremor. At 4×10^{-7}, 2×10^{-6}, and 1×10^{-5} mol per mouse the onset times were: 6, 3 and 1 min respectively. The duration of tremor for a dose of 4×10^{-7} mol was approximately 1·5 h, for 2×10^{-6} mol approximately 3 h, while for 1×10^{-5} the mice exhibited convulsions and died within 2·5 h.

The tremorgenic effects of SAM can be reversed with DL-dopa, the amino acid precursor of dopamine, and with cycloleucine, an agent that depletes SAM (Taylor & Randall, 1975). Each compound was injected intracerebroventricularly with 4×10^{-7} mol of SAM. A dose of 5×10^{-7} mol of DL-dopa decreased the intensity and the duration of the tremors and $1{\cdot}5 \times 10^{-6}$ mol aborted the tremors. Doses of 1×10^{-9} and 1×10^{-8} mol of cycloleucine also decreased the intensity and duration of tremors, and 1×10^{-7} and 1×10^{-6} mol prevented tremors. With the latter two doses, however, the mice appeared sedated and displayed a hump-back stance. With an intraperitoneal injection of 200 mg kg^{-1} of cycloleucine 1·5 h before SAM, the tremors ordinarily observable with 4×10^{-7} mol of SAM were substantially inhibited.

SAM is a cofactor in the metabolism of biogenic amines and therefore serves to reduce dopamine. A corpus striatum deficiency of biogenic amines, in particular dopamine, is common to patients with Parkinson's disease (Hornykiewiez, 1966). This observation coupled with the fact that tremors occur in patients with the disease and in mice injected with SAM, suggests a possible role for SAM in the disease's symptomology.

Under abnormal conditions, accumulation and/or increased synthesis of SAM in the brain could, conceivably, precipitate motor dysfunction by decreasing dopamine. SAM would be stoichimetrically utilized in the reaction process as illustrated below (Scheme 1). In view of the above consideration, the application of L-dopa in treating Parkinson's disease would be beneficial for two reasons: Not only would dopamine concentrations be increased, but decrease in the concentration of SAM might also be expected because of its increased use as a methyl donor. The administration of L-dopa to rats in doses approximating those used to treat patients with Parkinson's disease markedly decreased the concentrations of SAM in the brain and adrenals. This decrease coincided with increased urinary concentrations of 3-*O*-methyl-dopa, a SAM-dependent metabolite of dopa (Wurtman & Rose, 1970; Ordonez & Wurtman, 1973). Messiha, Hsu & Bianchine (1972) have also shown that the systemic administration of an aromatic L-amino acid decarboxylase inhibitor to enhance brain accessibility of L-dopa in treated patients resulted in a three-fold increase of 3-*O*-methyldopa and



Scheme 1

* Correspondence.

this was accompanied by an increase in the anti-Parkinson effect of L-dopa. Since increased concentrations of 3-*O*-methyldopa have been shown to be associated with decreased SAM during administration of L-dopa (Ordonez & Wurtman, 1973) the possibility that a reduction in SAM may also be related to the anti-Parkinson effect of L-dopa should be considered.

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Actions of propranolol on 5-HT receptors of snail neurons

G. A. COTTRELL*, P. COBBETT, *Wellcome Laboratories of Pharmacology, Gatty Marine Laboratory and Department of Physiology and Pharmacology, University of St. Andrews, Fife, U.K.*

The β-antagonist propranolol specifically interacts in low concentrations to block binding of 5-hydroxytryptamine (5-HT, serotonin) to a membrane fraction of rat brain homogenate, suggesting that it may block 5-HT receptors (Middlemiss, Blakeborough & Leather, 1977). Propranolol is known to have central effects in man, including anti-anxiety and anti-schizophrenia activity, and these effects could result from an action on 5-HT transmission (Green & Grahame-Smith, 1976).

To investigate further whether propranolol can in fact selectively effect transmission at serotoninergic (5-HT releasing) synapses, it is necessary to test the action of the drug on the intracellularly recorded electrical activity of neurons which receive a serotoninergic input. Such experiments are difficult in the mammalian brain for technical reasons. An alternative approach is to use a simpler preparation. One such preparation comprises part of the c.n.s. of the snail *Helix pomatia*, and also *Aplysia*, incorporating two readily located, symmetrical, giant 5-HT neurons and their follower neurons. Excitatory or inhibitory responses are recorded from different specified neurons when one of the 5-HT neurons is stimulated and the responses are mimicked with applied 5-HT (Cottrell & Macon 1974; Gerschenfeld & Paupardin-Tritsch 1974).

We have tested the effects of propranolol on the responses of these follower neurons to iontophoresed 5-HT, in *Helix pomatia*. Initial experiments showed that the drug antagonized the depolarizing responses to 5-HT (on the M cell) without affecting the 5-HT hyperpolarizing response. Even at 2×10^{-4}M, propranolol did not alter the input resistance or the firing pattern of the follower neurons, nor did it have any obvious local anaesthetic effect.

However, subsequent experiments showed that the same concentrations of propranolol also antagonized the depolarizing, but not the hyperpolarizing action of acetylcholine on other identified neurons. A similar effect was observed on dopamine responses. Further, unlike the binding studies of Middlemiss & others (1977) in which (−)-propranolol was approximately 60 times more potent than its (+)-isomer, blockade of the depolarizing 5-HT responses was equally effective with each isomer.

Thus propranolol does not act as a stereospecific, selective, 5-HT antagonist on these snail neurons. The effect of blocking depolarizing but not hyperpolarizing responses, may result from a direct action on transmitter activated, depolarizing, ionic channels, as has been suggested to account for a similar effect of curare on molluscan neurons (Carpenter, Swann & Yarowsky 1977).

It remains to be shown whether propranolol antagonizes iontophoresed 5-HT responses at neurons receiving serotoninergic input in the mammalian brain.

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* Correspondence.

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