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J. Pharm. Pharmacol. 1987, 39: 71–72
Communicated June 12, 1986

Letter to the Editor

Inhibition of amphetamine-induced locomotor activity by *S*-(+)-apomorphine: comparison with the action of *R*-(−)-apomorphine

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Saari et al in 1973, reported the synthesis of the *S*-(+) isomer of apomorphine [*S*-(+)-APO] as well as indicating that the isomer was inactive in producing postural asymmetries in mice in which the caudate had been unilaterally lesioned. However, our laboratories have shown that *S*-(+)-APO is an effective antagonist of *R*-(−)-apomorphine [*R*-(−)-APO]-induced stereotyped verticalization (Riffee et al 1982) with an ED50 of 7·7 mg kg^{-1} (observed during the inhibition of the action of 5 mg kg^{-1} *R*-(−)-APO). Thus, the potency of *S*-(+)-APO in blocking stereotypic activity is similar to that by which *R*-(−)-APO induces such behaviour. Recently we have used the amphetamine-stimulated locomotor model (Riffee & Wilcox 1985) to demonstrate that *R*-(−)-APO has activity presynaptically which results in the inhibition of the activity of the amphetamine. The present study was conducted to investigate the action of the *S*-(+)-APO isomer in comparison with the action of *R*-(−)-APO on amphetamine-stimulated locomotor activity.

The naive male albino CD-1 mice, 20–30 g, used had continual access to food and water but were food-deprived 24 h before testing. A 12 h light/dark cycle (lights on at 0700 h) was maintained and all testing was done between the hours of 0900 and 1700 h. Drugs used in the experiment were *R*-(−)-APO (MacFarland Smith, Edinburgh, Scotland), *S*-(+)-APO (Research Biochemicals, Wayland, Mass.) and amphetamine sulphate (Sigma, St Louis, MO). Drugs were prepared without preservatives immediately before use.

Locomotor activity was measured as described earlier (Riffee & Wilcox 1985) using Digiscan infrared activity monitors (Omnitech Electronics, Columbus, OH). All animals were pretreated with saline (0·9% NaCl) and given a 1 h habituation to the test chambers. The mice were then administered amphetamine (2·5 mg kg^{-1}) and returned to the test environment. Fifteen minutes later, half of the mice received *S*-(+)-APO or *R*-(−)-APO and the other half received saline. Locomotor activity was recorded for an additional 45 min. Data from the detectors represented actual distance travelled (in inches) per 5 min period. A microprocessor, programmed by the manufacturer (Omnitech), integrates the various angles in which the animal moves so that actual distance travelled can be determined. Sequential infrared beams must be interrupted for distance travelled to be registered. Continuous interruption of one beam by a behaviour such as head-bobbing would not be recorded as horizontal movement. Data analysis was done using analysis of variance with appropriate post hoc tests for significance (Wilcox et al 1979).

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Fig. 1 shows the dose-response for *R*-(−)-APO and *S*-(+)-APO-induced inhibition of amphetamine-stimulated locomotor activity. The ED50 was calculated for each isomer based on the inhibition of the maximum locomotor stimulation induced by 2·5 mg kg^{-1} amphetamine administration. The ED50 for *R*-(−)-APO was 0·018 mg kg^{-1} while the ED50 for *S*-(+)-APO was calculated to be 0·468 mg kg^{-1}, a 26-fold difference. In this behavioural model, both isomers acted similarly in that they significantly decreased the maximum effect of the amphetamine. A previous study in our laboratories showed that, in the murine stereotypic verticalization model, the *S*-(+)-APO had agonist properties while the *R*-(−)-APO isomer was an agonist (Riffee et al 1982). Biochemical analyses were done to determine whether the effect of *S*-(+)-APO observed in the present experiment was pre or postsynaptic in nature. We found that *S*-(+)-APO reversed the γ-amino-butyrolactone (GBL)-induced increase in L-dopa accumulation in the nucleus accumbens in much the same manner as *R*-(−)-APO (data not shown). Thus, it appears that the inhibitory action of *S*-(+)-APO may be associated with a presynaptic site. Shen et al (1984) showed that *S*-(+)-APO and *R*-(−)-APO were equipotent as noncompetative inhibitors of dihydropteridine reductase, an enzyme important in the in-vivo hydroxylation of tyrosine, and thus potentially inhibitors of catecholamine release. They argued that the lack of a difference in inhibitory concentrations found in their study suggested that the interaction was not dependent on binding to a stereoselective site on the enzyme. Taken together these data suggest that the apomorphine isomers may be acting presynaptically. However, the differences in behavioural potencies shown in the amphetamine-stimulated locomotor activity model in this study compared with the similar potencies in the in-vitro dihydropteridine study, suggest that in our model, there is some degree of stereoselectivity occurring, perhaps at a tyrosine hydroxylase regulatory site.

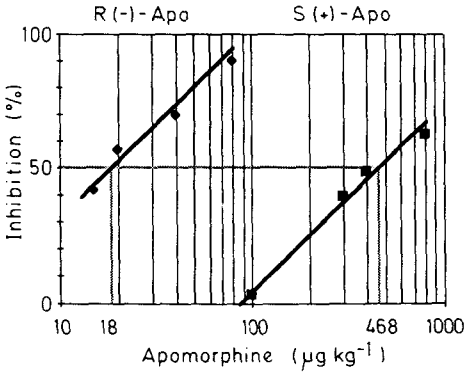

FIG. 1. Dose-response relationship for *R*-(−)-APO and *S*-(+)-APO inhibition of amphetamine-stimulated locomotor activity. The percent inhibition (y-axis) of amphetamine (2·5 mg kg^{-1})-stimulated locomotor activity induced by the two isomers is plotted against the log of the doses (μg kg^{-1}; x-axis) used. The data were calculated from means of 20 separate experiments using no fewer than 12 animals per experiment. The standard error of the mean was ≤10% of the mean in all instances.

Similar properties have been shown for other dopaminergically active drugs such as the enantiomers of the dopamine analogue 3-(3-hydroxyphenyl)-*N*-n-propylpiperidine (3-PPP). These isomers of 3-PPP have been shown to have the opposite effects on postsynaptic dopamine receptors; the (+)-isomer acts as an agonist and the (−)-isomer exhibits properties of an antagonist (Oberlander & Boissier 1983) similar to our finding earlier that *S*-(+)-APO blocks the stereotypic actions of *R*-(−)-APO. Furthermore, the two 3-PPP isomers appear to act as agonists at striatal and limbic dopamine autoreceptors controlling dopamine synthesis (Clark et al 1984) similar to the behavioural findings of the present study. However, those authors reported that the 3-PPP effects were reversible with haloperidol thus substantiating their claims that the interaction involves autoreceptors. No such antagonism by haloperidol of the inhibition of amphetamine-stimulated locomotor activity by the APO isomers was observed in the present study (unpublished results).

There exists an apparent 26-fold difference in the agonist potencies for the *S*-(+)-APO and *R*-(−)-APO isomers in the amphetamine-stimulated locomotor behavioural model. However, it should be kept in mind that the ED50 for *S*-(+)-APO is only 0·468 mg kg^{-1} so a presynaptic site of action for *S*-(+)-APO is a strong possibility. Unlike what was found in earlier studies, this isomer of apomorphine has been shown to be significantly active pharmacologically in two types of behaviour thought to be primarily dopaminergic in nature.

These studies were supported by a grant from the National Institute of Mental Health (MH 33442) to W. Riffee and R. Wilcox and by a BRSG grant to W. Riffee.

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