J. Pharm. Pharmacol. 1985, 37: 930–931
Communicated July 8, 1985

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Ascorbic acid antagonizes the behavioural effects of LSD in cats

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Pretreatment with ascorbic acid (500 mg kg^{-1} i.p.) antagonized the behavioural effects of lysergic acid diethylamide (LSD) and apomorphine, but not 5-methoxy-*N,N*-dimethyltryptamine, in cats. The data support the hypothesis that these behavioural effects in cats are due to drug action at both 5-HT and dopamine receptors, and that the action of LSD at dopamine receptors is modulated by ascorbic acid.

The mechanism of action of lysergic acid diethylamide (LSD) and related hallucinogens has been investigated for more than three decades. LSD was originally hypothesized to act by suppressing the activity of the central 5-HT system (Aghajanian et al 1970). However, more recent data have suggested that LSD and related hallucinogens may exert their effects, at least in part, by an agonist action at post-synaptic 5-HT receptors in the central nervous system (Trulson 1985). It has also been hypothesized that LSD exerts its effects in part by an action at central dopamine receptors (e.g. Trulson & Crisp 1982). We suggested that hallucinogens may exert their effects by a combined action at both post-synaptic 5-HT and dopamine receptors (Trulson 1985).

Ascorbic acid has recently been shown to alter the activity at central dopamine receptors (e.g. Rebec et al 1985) but ascorbic acid does not appear to affect 5-HT receptors. Therefore, we have examined the effects of pretreatment with ascorbic acid on the behavioural effects of LSD, apomorphine, and 5-methoxy-*N,N*-dimethyltryptamine (5-MeODMT) in the cat.

Administration of LSD and related drugs to cats elicits a variety of behavioural signs consisting primarily of limb flicking and abortive grooming (Trulson 1985). The limb flick and abortive groom are useful model behaviours for studying the actions of LSD and related drugs, particularly when quantitative data are desired.

Methods

Cats were pretreated with ascorbic acid (500 mg kg^{-1} i.p., 30 min before the test drug), and were then administered either LSD (50 μg kg^{-1} i.p.), apomorphine (4 mg kg^{-1} i.p.) or 5-MeODMT (100 μg kg^{-1} i.m.) and behaviour was monitored for 1 h post-injection.

Additional groups of cats (n = 3) were given saline or ascorbic acid followed by LSD, apomorphine or 5-MeODMT, at the doses described above, and were then anaesthetized with chloral hydrate (350 mg kg^{-1} i.p.) 30 min following LSD, and 15 min following apomorphine and 5-MeODMT. The brains were rapidly removed and the right half-brains assayed for either LSD using the method of Axelrod et al (1957), apomorphine using the method of Symes et al (1975), or 5-MeODMT using HPLC with electrochemical detection as previously described (Trulson & Keltch 1985).

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Results

The data revealed that pretreatment with ascorbic acid greatly attenuated LSD- or apomorphine-induced behaviours, while 5-MeODMT-induced behavioural changes were not altered by ascorbic acid pretreatment (Table 1). Neurochemical analysis revealed that pretreatment with ascorbic acid did not alter the uptake of LSD (23·1 ± 2·7 vs 26·4 ± 1·9 ng g^{-1} in control animals), apomorphine (3·1 ± 0·4 vs 2·8 ± 0·3 μg g^{-1} in control animals), or 5-MeODMT (1·2 ± 0·1 vs 1·5 ± 0·2 ng g^{-1} in control animals) into the brain.

Table 1. Effects of ascorbic acid on hallucinogens-induced behaviours.

	Behaviour	
Treatment	Limb flick	Abortive groom
Saline	0·1 ± 0·1	0·0 ± 0·0
Saline + LSD (50 μg kg^{-1})	38·4 ± 4·8[a]	5·2 ± 0·9[a]
AA + LSD (50 μg kg^{-1})	12·4 ± 2·1[a,b]	0·7 ± 0·4[b]
(% change)	(−67·7%)	(−86·5%)
Saline + APO (4 mg kg^{-1})	36·3 ± 5·9[a]	4·7 ± 0·9[a,b]
AA + APO (4 mg kg^{-1})	7·9 ± 1·8[a,b]	0·0 ± 0·0[b]
(% change)	(−78·2%)	(−100%)
Saline + 5-MeODMT (100 μg kg^{-1})	23·7 ± 5·3[a]	2·8 ± 0·6[a]
AA + 5-MeODMT (100 μg kg^{-1})	26·2 ± 4·0[a]	3·2 ± 0·8[a]
(% change)	(+10·5%)	(+14·3%)

Values are presented as means ± s.e.m.s for 6 cats. % change values represent change from saline + drug vs AA + drug for each of the three drugs.

[a] Significantly different from control (saline) values, $P < 0·01$ Dunnett's tests.

[b] Significantly different saline + drug, $P < 0·01$ two-tailed *t*-tests.

Discussion

The present data support the hypothesis that the action of LSD in cats is mediated by an action at both 5-HT and dopamine receptors. The results are not likely to be due

to a metabolic or pharmacokinetic interaction between ascorbic acid and LSD and/or apomorphine, since ascorbic acid acts as an antioxidant and, should such a metabolic or pharmacokinetic interaction occur, one would expect the opposite effect, i.e. that ascorbic acid pretreatment would potentiate the effects of LSD and/or apomorphine. Ascorbic acid has been shown to be an essential ingredient in assays demonstrating a high affinity binding of dopamine antagonists, such as haloperidol, to dopamine binding sites in-vitro (Leff et al 1981). The effect of ascorbic acid on the binding of dopamine agonists, on the other hand, would be expected to produce the opposite effect. It is noteworthy that megavitamin therapy including very large doses of ascorbic acid have been shown to be effective in treating certain forms of schizophrenia (Pauling 1974), which appears to be due to the over-stimulation of dopamine receptors in the forebrain.

The fact that pretreatment with ascorbic acid does not change the behavioural response to 5-MeODMT is consistent with the finding that ascorbic acid does not appear to interact with 5-HT binding sites. These latter data also support the hypothesis that the inhibitory effects of ascorbic acid on LSD- and apomorphine-induced behaviours in the cat are not due to a general depression of behaviour by ascorbic acid. This hypothesis is further substantiated by the fact that ascorbic acid alone produced no significant behavioural changes in these animals.

In conclusion, our data support the hypothesis that LSD and related hallucinogens act by a combined action at central 5-HT and dopamine receptors. The fact that LSD-induced behaviours are partially blocked by ascorbic acid suggests that large doses of ascorbic acid may be a new method for treating LSD overdose.

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J. Pharm. Pharmacol. 1985, 37: 931–932
Communicated October 4, 1985

© 1985 J. Pharm. Pharmacol.

Letter to the Editor

A hypothesis for the mode of action of anti-rheumatic drugs in a model of cartilage destruction

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We have been using as a model rats and mice with air pouches which develop lining cells closely resembling synovium (Edwards et al 1982; Sedgwick et al 1983). These pouches when sufficiently mature, i.e. 6 days, will respond to a variety of stimuli both immune and non-immune with long lasting exudates containing many migrated leucocytes (Sedgwick et al 1983, 1984a).

We examined the breakdown of cartilage in both inflamed and non-inflamed pouches and have found that inflammation protected the rate of loss of proteoglycan from cartilage (Sedgwick et al 1984b, 1985; Willoughby et al 1985). Invariably the cartilage in the inflamed air pouch would float free in exudate while cartilage, in the non-inflamed pouch would adhere to the pouch wall in close proximity to the macrophages and fibroblasts of the lining cells. Unpublished findings from this department (de Brito) have shown that the presence of granulation tissue in close proximity to cartilage will speed proteoglycan loss.

Implantation of rat femoral head cartilage into pouches of rats treated with indomethacin (3 mg kg^{-1}) showed protection against loss of proteoglycan, unlike xiphisternum cartilage which showed no protection (Sin et al 1984; Sedgwick et al 1984b). This drug treatment caused suppression both of cells and volume of exudate in inflammation induced by carrageenan. It seems unlikely that the protection afforded by indomethacin could be due to its anti-inflammatory effect since this would be expected to enhance cartilage breakdown. A more likely explanation could be that in granulomatous inflammation indomethacin has previously been shown to induce macrophages to engage in autophagocytosis, where lysosomes are seen adjacent to mitochondria, fusing with them (Di Rosa et al 1971). This self-

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