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Atropine reversal of kainic acid-induced decrease in the leptazol convulsive threshhold

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A growing body of evidence suggests that a close relationship exists between the intracerebroventricular or subcutaneous administration of kainic acid (KA), a neurotoxic analogue of glutamic acid, and seizure activity (Ben-Ari et al 1979; Kleinrok et al 1980a). An effect of KA on the seizure threshold can be detected immediately after its administration but that acid may elicit behavioural consequences over longer periods. Thus it has been reported that mice exhibit a decrease in the threshold for leptazol-induced seizures on the 5th day after a single intracerebroventricular injection of KA (Kleinrok et al 1980b). The present study was undertaken to clarify the mechanism responsible for the observed phenomenon.

Experiments were carried out on Albino Swiss male mice (18–22 g). KA (Sigma) was dissolved in 0·15 M phosphate buffer (pH—7·2) and administered intracerebroventricularly in a dose of 0·1 μg per mouse and in a volume of 1 μl according to Herman (1975), Leptazol (pentetrazol, Cardiazolum; Polfa) and atropine sulphate (Polfa) were dissolved in distilled water, leptazol being given subcutaneously and atropine—intraperitoneally in a dose of 10 mg kg^{-1}, 60 min before the leptazol). The convulsive test was on the 5th day after the single injection of KA. Leptazol-injected animals were observed for the occurrence of clonic and tonic seizures within 30 min of the time of leptazol injection. The observations were 'double blind'. The convulsive threshold was evaluated as the ED50 (in mg kg^{-1} of leptazol). Both ED50 values and statistical analysis of the results were calculated according to Litchfield & Wilcoxon (1949).

Intracerebroventricular injections of KA produced a decrease in the convulsive threshold for both clonic and tonic phases of leptazol-induced seizures which was in good agreement with the results previously obtained (Kleinrok et al 1980b). Atropine 60 min before leptazol reversed this effect in the KA-injected mice, raising ED50 values from 54 to 64 mg kg^{-1} in the clonic phase, and from 70 to 80 mg kg^{-1} in the tonic phase. Atropine itself was without influence on the convulsive threshold (Table 1). This lack of effect was also found by Stone et al (1960). These results suggest that the cholinergic system is generally not involved in convulsive reactions brought about by leptazol in normal mice.

The KA-induced decrease in the threshold may be discussed on the basis of probable disturbances in the inhibitory processes controlling cholinergic activity in the septal-hippocampal pathway as the toxic affinity of KA to the hippocampal pyramidal cells has been well established (Nadler et al 1978; Ben-Ari et al 1979). The long-term proconvulsive effect of KA might thus be dependent on disruption of the hippocampal pyramidal pathway, innervating the septal cholinergic cells which project to the hippocampus via GABA-ergic interneurons. The partial liberation of these cholinergic neurons from GABA-ergic inhibitory control, which is modulated by the glutamatergic pyramidal hippocampal cells, might be relevant for the KA long-term proconvulsive effect. Also, cholinergic stimulation itself may result in convulsions (Longo 1966; Maynert 1969). However, there are no changes in acetylcholine turnover in hippocampa of KA-lesioned rats (Wood et al 1979) which clearly indicates the lack of spontaneous cholinergic hyper-activity in the septal-hippocampal pathway under such conditions. It might therefore be

Table 1. Influence of atropine on the kainic acid (KA; 0·1 μg per mouse)-induced decrease in the leptazol convulsive threshold (95% confidence limits in parentheses).

Group	Treatment	N[a]	ED50 of leptazol (in mg kg^{-1}) clonic phase	$P <$	tonic phase	$P <$
I	None[b]	73	67 (62–72)	—	83 (76–91)	—
II	KA	66	54 (49–60)	0·05 (II/I)	70 (65–75)	0·05 (II/I)
III	Atropine (10 mg kg^{-1})	73	66 (60–73)	0·05 (III/II) NS (III/I)	77 (71–84)	NS (III/II) NS (III/I)
IV	KA + Atropine (10 mg kg^{-1})	59	64 (59–70)	0·05 (IV/II) NS (IV/I)	80 (76–85)	0·05 (IV/II) NS (IV/I)

[a] number of animals used to calculate one ED50 value.
[b] control animals received intracerebroventricular injections of 0·15 M phosphate buffer only.

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that in the KA-injected animals the septal cholinergic cells, deprived of the feed-back inhibition, are more sensitive to stimulatory effects of leptazol which probably leads to the greater susceptibility to this convulsant. Atropine reversal of the proconvulsive effect of KA seems to confirm the above hypothesis.

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Effect of monoamine oxidase inhibitors on codeine disposition and pentobarbitone sleep-times in the rat

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Monoamine oxidase inhibitors (MAOIs) have been observed to cause adverse reactions in patients who are also being treated with one of a number of other therapeutic agents (Goldberg 1964; Sjoqvist 1965). Particularly severe reactions have been seen with the analgesic, meperidine, when the MAOI has been phenelzine (Taylor 1962) or pargyline (Vigran 1964).

A degree of controversy has existed over the scientific basis of this particular drug interaction. Various animal studies have shown that meperidine metabolism is inhibited in vitro (Clark 1967; Clark & Thompson 1972) and in vivo (Eade & Renton 1970), and that the LD50 of meperidine in mice was reduced by phenelzine pretreatment (Eade & Renton 1970). Recently, the analgesia caused by meperidine in the rat has been reported to be potentiated by pargyline, and plasma and brain meperidine concentrations and urinary meperidine excretion were significantly higher in pargyline-treated animals (Yeh et al 1979), again indicating alterations in disposition of meperidine. Other reports have concluded that the increased toxicity of potent analgesics in combination with MAOIs is not due to decelerated metabolism of the analgesic, but is related to concentrations of cerebral 5-hydroxytryptamine (Rogers & Thornton 1969; Gessner & Soble 1973). Adverse effects have seldom been observed in patients to whom morphine and MAOIs have been administered concomitantly. However, acute pargyline pretreatment was found to potentiate morphine analgesia in rats (Yeh & Mitchell 1971), probably due to inhibition of morphine glucuronidation (Yeh & Mitchell 1972a), while chronic pargyline pretreatment decreased morphine analgesia probably because of enhanced morphine glucuronidation (Yeh & Mitchell 1972b).

The scope of such interactions between MAOIs and other therapeutic agents has not been explored extensively nor have clinically-meaningful MAOI doses been studied. Consequently, the relevance of these observations to the therapeutic use of MAOIs is difficult to evaluate. The doses which were chosen for study were far in excess of those required to produce 100% inhibition of MAO. This communication presents preliminary results on the interaction of codeine, an analgesic widely prescribed for relief of moderate pain, with various MAOIs which were administered as single doses sufficient for 80% inhibition of MAO (IC80) *in vivo in rats at 1 h after dosing (Leighton et al 1979).* The IC80 for MAO inhibition is thought to correlate with antidepressant efficacy in man (Christmas et al 1972). Data on the interference of these agents with pentobarbitone metabolism, as measured by duration of hypnosis, are also presented. With the exception of clorgyline, the MAOIs studied inhibit non-specifically and irreversibly both A- and B-MAO activity. Clorgyline is a specific, irreversible A-site inhibitor.

Groups of male Sprague-Dawley rats 180–200 g (Charles River Laboratories, N.Y.) were treated with daily injections of 0·9% NaCl (saline) (0·5 ml), tranylcypromine sulphate (2 mg kg^{-1}; Smith Kline and French Labs, Philadelphia, Pa.), clorgyline hydrochloride (2 mg kg^{-1}; May and Baker Co., Dagenham, U.K.), pargyline hydrochloride (20 mg kg^{-1}; Sigma Chemical Co., St. Louis, Mo.) or phenelzine hydrochloride (7 mg kg^{-1}; Warner-Lambert, Ann Arbor, Mi.), all MAOIs being administered i.p. in saline (0·5 ml). One hour after the fifth daily injection, each group of

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