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An interaction between hydrocortisone and hemicholiniums in mice

Toxicity of hemicholinium-3 (HC-3) has been attributed to failure of acetylcholine synthesis due to interference with the passage of choline to its intracellular sites of acetylation (MacIntosh, Birks & Sastry, 1958; Gardiner, 1961). The work of Schueler (1955) and Reitzel & Long (1959), who have reported that choline is the specific antagonist to HC-3 toxicity, supports this. Perfusion studies on the cat superior cervical ganglion have shown that the presence of choline in the perfusion fluid is essential for optimal synthesis and release of acetylcholine and that acetylcholine synthesis is inhibited by HC-3 (Birks & MacIntosh, 1961). Drugs which can influence the plasma levels of choline might therefore be expected to modify the toxicity of HC-3. Cortisone has been reported to lower the plasma choline of dogs by 60–80% within 30 min of injection (MacIntosh, 1963). We now report the effects of a water-soluble hydrocortisone derivative (hydrocortisone sodium succinate) on the toxicity in mice of HC-3 and its *p*-terphenyl analogue (TPHC-3) (Gardiner & Lee, 1969).

Albino mice of either sex weighing 16–24 g were used. The mice were pretreated with hydrocortisone (10 mg/kg) or 0·9% sodium chloride (saline). One h later the mice were injected with different doses of HC-3 or TPHC-3. 20 mice were used for each dose.

All drugs were made up in saline and administered by intraperitoneal injection. The volume of drug solutions injected was 0·1 ml per 10 g mouse. The number of mice that died at the end of 2 h were noted.

The mortality in mice increased with increasing doses of HC-3 and TPHC-3 (Table 1). TPHC-3 was the more toxic (Gardiner & Lee, 1969). Pretreatment with hydrocortisone (10 mg/kg) for 1 h reduced the mortality produced by all doses of HC-3 and TPHC-3.

It was anticipated that, if hydrocortisone produced a fall in plasma choline, as

Table 1. *Partial protection of mice against HC-3 and TPHC-3 by pretreatment with hydrocortisone* (10 mg/kg). Hydrocortisone or saline was administered 1 h before HC-3 or TPHC-3. The values given are % mice dead 2 h after injecting HC-3 or TPHC-3 (20 mice/group) and each value represents the mean ± s.e. of four experiments.

HC-3			TPHC-3		
Dose (μg/kg)	Animals receiving: hydrocortisone	saline	Dose (μg/kg)	Animals receiving: hydrocortisone	saline
120	16 ± 2	29 ± 4	80	10 ± 5	19 ± 6
150	33 ± 3	53 ± 9	100	16 ± 5	45 ± 8
180	55 ± 3	70 ± 5	120	63 ± 3	76 ± 4
220	81 ± 3	90 ± 0			

it was reported to do in dogs (MacIntosh, 1963), it might enhance the toxicity of the hemicholiniums. However, it was found that hydrocortisone protected the mice to a small extent from the toxicity of the hemicholiniums.

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[^{3}H]Dopa in [^{3}H]tyrosine with high specific activity: a serious complication in the study of catecholamine metabolism

Decomposition by self-irradiation is a great problem for users of tritium-labelled compounds. Although some factors controlling the stability of labelled compounds have been elucidated, much is unknown and stored compounds may suddenly show a markedly accelerated rate of decomposition (cf. Bayly & Evans 1966, 1967).

In many cases traces of an impurity may be relatively harmless. If, however, it interacts with chemical or biochemical processes to be studied, the result may lead to serious misinterpretations. It has been shown that one of the radiolysis products of tyrosine is dopa (Rowbottom 1955). The present report will demonstrate the effect of traces of [^{3}H]dopa in [^{3}H]tyrosine when studying the catecholamine metabolism using [^{3}H]tyrosine.

In the following experiment the [^{3}H]tyrosine* used was found by radiopaper chromatography (isopropanol–2N HCl, 65 : 35, v/v) to contain about 12% impurities, more than half of which could be identified with dopa.

^{3}[H]Tyrosine, 5 μg/kg weight, was given intravenously to male rats grouped in pairs. Fifteen min later the animals were killed. [^{3}H]Noradrenaline (^{3}H-NA) and [^{3}H]dopamine (^{3}H-DA) in the caudate nucleus, the spinal cord and in the heart were determined, after separation on alumina and Dowex 50 columns (for details see Persson & Waldeck 1968, Persson 1969). The results are presented in Table 1. This Table also shows results obtained from pure [^{3}H]tyrosine and [^{3}H]dopa in a previous investigation (Persson 1969) under experimental conditions similar to those described above. From these values the expected yield of ^{3}H-NA and ^{3}H-DA from [^{3}H]tyrosine containing 10%[^{3}H]dopa has been calculated. It appears that the values obtained in the present experiment in four out of six cases are rather close to these calculated values. ^{3}H-NA in the caudate nucleus and ^{3}H-DA in the spinal cord were considerably higher than would be expected. These irregularities may be caused by decomposition products other than [^{3}H]dopa.

* L-Tyrosine, ring-3,5-^{3}H in an aqueous solution containing 2% ethanol, specific activity 47 Ci/mmol, was obtained from The Radiochemical Centre, Amersham.