The results demonstrate the general similarity between the muscarinic receptors mediating inhibition of noradrenaline release, atrial tension development and ventricular frequency. In particular, by analogy with sites in the sympathetic ganglion, inhibition of noradrenaline release is more likely to be the result of muscarinic-induced hyperpolarization than depolarization, and McNeil-A-343 and AHR 602 show relative specificity for the receptors (Trendelenburg, 1967).

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Demethylation of 3-*O*-methyldopa

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It has recently been shown that administration of L-3-*O*-methyl,4-hydroxyphenylalanine (3-*O*-methyldopa; 'OMD'), a major metabolite of L-dihydroxy-phenylalanine (L-dopa), leads to the formation of dopamine in the rat brain (Bartholini, Kuruma & Pletscher, 1971). These authors suggest that the increase is the result of initial demethylation of OMD to L-dopa which is then decarboxylated to dopamine, since OMD is a poor substrate for decarboxylation and does not appear to be directly converted to 3-*O*-methyldopamine in appreciable quantities either *in vitro* (Ferrini & Glasser, 1964) or *in vivo* (Bartholini, Kuruma & Pletscher, 1971).

In *O*-demethylation the methyl group is oxidized, via formaldehyde, to carbon dioxide which is eliminated in expired air. Thus, in order to measure directly the extent and rate of *O*-demethylation we have enzymatically synthesized methyl labelled ^{14}C-OMD from L-dopa, using a partially purified catechol-*O*-methyl transferase (Axelrod & Tomchick, 1958) and S-adenosylmethionine (methyl-^{14}C). One microcurie of ^{14}C-OMD was given intraperitoneally to rats maintained in an airtight chamber ('Metabowl'—Jencons) permitting continuous collection of expired CO_2, urine and faeces. After a delay of about 4 h radioactivity began to be excreted slowly as ^{14}C-CO_2 in the expired air. A total of 15–20% of the dose was recovered in the expired air over 3–4 days, thus directly demonstrating that a significant fraction of the administered OMD is demethylated *in vivo*. During the same period 65% of the dose was excreted in the urine and 8% in faeces. We were unable to demonstrate oxidative demethylation of OMD by liver or brain *in vitro*, even though it is well established that liver preparations can *O*-demethylate several foreign compounds (Gillette, 1966). Since the initial delay and slow rate of excretion of ^{14}C-CO_2 might have been due to demethylation of OMD in the gut after excretion in the bile, experiments were repeated in rats with biliary fistulae. In these animals 20% of the dose was excreted in the bile during the

first 24 hours but there was no excretion of ^{14}C-CO_2 in expired air. These experiments establish that OMD is demethylated in rats *in vivo* and that the demethylation probably takes place in the gut.

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Comparison of effects exerted by isomers and analogues of (±)-2,3-dehydroemetine on protein synthesis in rat liver

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(±)-2,3-Dehydroemetine (DHE), an amoebicidal drug (Johnson & Neal, 1968) with potential in anticancer chemotherapy (Abd-Rabbo, 1969; Jondorf, Abbott, Greenberg & Mead, 1971), has been compared with (−)-emetine for its effects on hepatic protein synthesis in the rat (Jondorf, Drassner, Johnson & Miller, 1969). It was of interest to extend the previous studies with racemic DHE to the individual optical isomers in view of the finding in some biological systems (Johnson & Neal, 1968; Jondorf *et al.*, 1971) but not in others (Brossi, Baumann, Burkhardt, Richle & Frey, 1962) that (−)-DHE was about twice as active as the racemic compound.

We have now been able to show that the intraperitoneal administration of (±)-DHE or (−)-DHE to 160 g female Sprague-Dawley rats (of the same age) stimulates the uptake of ^{14}C-labelled L-amino acid into protein in a liver microsomal incorporating system *in vitro* (Jondorf *et al.*, 1969) in the same dose-dependent way when the incubations are carried out with subcellular fractions prepared 24 h after pretreatment with the drugs. Maximal stimulation of incorporation occurs at a pretreatment level of 18 μmoles/kg. When (±)-DHE or (−)-DHE are added directly to the amino-acid incorporating system *in vitro*, there is a progressive concentration dependent inhibition of amino-acid incorporation, which appears to be very similar for the racemic compound and the (−)-isomer.

In a third type of experiment, the incorporation of L-leucine into liver protein *in vivo* is inhibited to the same extent at 2 h after pretreating rats with equimolar doses of (±)-DHE or (−)-DHE in the range 1·8–18 μmoles/kg.

None of these effects are observed with (+)-DHE which is as inactive in these respects as (−)-isoemetine or (+)-*O*-methylpsychotrine (Jondorf *et al.*, 1969). This is not altogether surprising, since (+)-DHE, in common with these other inactive compounds, lacks the correct stereospecific alignment at the C-1′ position in the molecule thought to be decisive for biological activity (Grollman, 1966). What is surprising is that the above effects observed with (±)-DHE are not seen when the corresponding experiments are performed at similar or greater dose levels with the analogues NSC-134754 and NSC-134756 each lacking one pair of adjacent OCH_3 substituents

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