Thus in contrast to other studies we have found a stabilizing action of ibuprofen at 10^{-4} and 10^{-5}M on rat liver lysosomes, no effect of ibuprofen on free A.P. activity and an inhibition of free A.P. by 10^{-3}M prednisolone. Although significant, the stabilizing effect of these two drugs on rat liver lysosomes is slight and is unlikely to account for their full anti-inflammatory activity. Also it is curious that these *in vitro* effects of ibuprofen and prednisolone should be so similar in view of their differing potencies clinically.

University of Melbourne Department of Medicine,
Royal Melbourne Hospital,
Victoria 3350, *Australia.*

M. L. PHILLIPS
K. D. MUIRDEN

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Increased accumulation of [^{3}H]catecholamines formed from [^{3}H]dopa after treatment with caffeine and aminophylline

There is growing evidence that the methylxanthines, caffeine and theophylline affect the metabolism of cerebral catecholamines. An increased turnover of noradrenaline brought about by these drugs has been reported (Berkowitz, Tarver & Spector, 1970; Waldeck, 1971; Corrodi, Fuxe & Jonsson, 1972). Further, the turnover of brain dopamine appeared first to increase and then to decrease after the administration of caffeine (Waldeck, 1971; Corrodi & others, 1972). The present study shows that the accumulation of [^{3}H]catecholamines formed from [^{3}H]dopa in the brain and heart of the mouse increases after treatment with caffeine and aminophylline.

Female mice, about 20 g, received an intraperitoneal injection of 100 mg/kg caffeine or aminophylline 30 min before the intravenous injection of 20 μg/kg L-dopa ring-2,5,6-^{3}H (The Radiochemical Centre, Amersham). Control animals received [^{3}H]dopa only. Sixty min after the labelled dopa had been given the animals were killed by decapitation, their brains and hearts removed and extracted in perchloric acid. [^{3}H]Noradrenaline (^{3}H-NA) [^{3}H]dopamine, [^{3}H]normetanephrine and [^{3}H]methoxytyramine were isolated with a combination of alumina and Dowex 50 columns. The analytical procedure and the testing of the radiochemical purity of the labelled dopa has been described by Persson & Waldeck (1968, 1970).

Caffeine increased the net accumulation of ^{3}H-NA and [^{3}H]dopamine in the brain by 80 ($P < 0.01$) and 130 ($P < 0.001$) % respectively (Fig. 1) while aminophylline tended to increase their yields though less markedly ($0.10 > P > 0.05$ and $P < 0.05$ respectively). [^{3}H]Normetanephrine appeared to follow the same pattern as ^{3}H-NA, however, statistical significance was not obtained. [^{3}H]Methoxytyramine in the brain increased threefold in animals treated with caffeine ($P < 0.001$) but was unchanged by aminophylline.

In the heart, the accumulation of ^{3}H-NA increased by some 30% after both caffeine and aminophylline ($P < 0.005$). [^{3}H]Dopamine was slightly increased ($P < 0.005$ after caffeine). There were no significant changes in [^{3}H]normetanephrine while the [^{3}H]methoxytyramine level doubled after caffeine ($P < 0.01$).

An increased accumulation of [^{3}H]catecholamines formed from [^{3}H]dopa can be brought about in various ways, e.g. by an increased transport of dopa into the adrenergic neuron, by an increased rate of decarboxylation or, by a decreased metabolism of the amines formed. None of these alternatives can be ruled out in

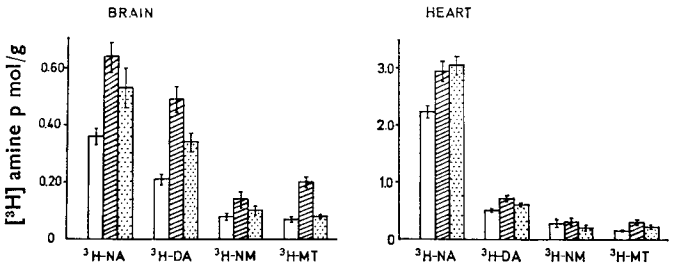

FIG. 1. Effect of caffeine and aminophylline on the accumulation of [^{3}H]amines formed from [^{3}H]dopa in the brain and heart of the mouse. Caffeine, 100 mg/kg or aminophylline, 100 mg/kg were given intraperitoneally to mice 30 min before the intravenous administration of 20 μg/kg [^{3}H]dopa. Control animals received [^{3}H]dopa only. After another 60 min the animals were killed and [^{3}H]noradrenaline (^{3}H-NA), [^{3}H]dopamine (^{3}H-DA), [^{3}H]normetanephrine (^{3}H-NM) and [^{3}H]methoxytyramine (^{3}H-MT) in brain and heart were determined. Shown are the mean $\pm$ s.e. of 4–6 experimental groups, each comprising 6 animals. Open columns, control; hatched columns, caffeine; dotted columns, aminophylline.

the present study. However, the increase in [^{3}H]normetanephrine and [^{3}H]methoxytyramine observed was almost proportional to the increase in ^{3}H-NA and [^{3}H]-dopamine respectively. Under similar experimental conditions a complete inhibition of the monoamine oxidase causes an increase in [^{3}H]methoxytyramine in the brain which exceeds the increase in [^{3}H]dopamine by a factor of a hundred. Inhibition of the catechol-*O*-methyl transferase is associated with a decrease in the *O*-methylated derivatives (Persson & Waldeck, 1969).

The methylxanthine-induced increase in [^{3}H]catecholamines was less pronounced in the heart than in the brain. A possible explanation for this difference is that newly synthesized amines in the heart are displaced by adrenaline, released from the adrenal medulla by the methylxanthines (Muscholl, Kiefer & Lindmar, 1969; Berkowitz & Spector, 1971). As is well known, adrenaline does not penetrate the blood-brain barrier of most brain regions.

Irrespective of the underlying mechanism, the increased accumulation of catecholamines from dopa brought about by the methylxanthines may have clinical implications. This suggestion is strengthened by some recent observations that caffeine increases the dopa-induced hypermotility in mice (Strömberg & Waldeck, unpublished).

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Department of Pharmacology,
University of Göteborg, Fack,
S-400 33 *Göteborg* 33, *Sweden.*

BERTIL WALDECK

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