As shown in Table I, values of bound Ca/Mg ratio in microsomes from various tissues incubated with ATP free medium did not differ. However, incubated with ATP containing medium, the ratio was increased. The increment was more marked in vas deferens and ileum, which were contracted by ATP, than in atria and taenia coli, which were relaxed. On the other hand, Mg^{++} -ATPase activity was higher in atria and taenia coli than in vas deferens and ileum, while Na^+ , K^+ -ATPase activity did not differ to any great extent.

It has previously been demonstrated that increase in Ca/Mg ratio of the medium enhanced the contractile response to ATP of the isolated smooth muscle (8). Moreover, with regard to contractile response of ATP, it has been postulated that exogenously applied ATP may increase Ca/Mg ratio in the cell membrane, thereby favoring Ca entry and contraction (2). Present data appear to support the postulation. From present findings, it may be considered that in excitatory tissues, exogenously applied ATP is hydrolyzed very little and directly acts on the membrane, thereby favoring increase in Ca/Mg ratio, while in inhibitory tissues it is easily hydrolyzed and adenosine-like action of ATP is intensified.

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EFFECTS OF 5-HYDROXYINDOLEACETIC ACID ON ISOLATED CANINE CEREBRAL ARTERIES

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Recent study in this laboratory has demonstrated that 5-hydroxykynurenamine (5-HK) (1), converted from serotonin by tryptophan 2, 3-dioxygenase (2) and formamidase, causes contractions of isolated canine cerebral arteries as does serotonin, and also attenuates the vascular response to serotonin (3). 5-Hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin (4) via a catalysis of monoamine oxidase, has been shown to possess no or only slight serotonin-like activity in a variety of organs and tissues (5-7); however, little is known concerning interactions of this metabolite with serotonin ac-

tion. The present study was thus undertaken to investigate the effect of 5-HIAA and its interaction with serotonin in isolated canine cerebral arteries.

Basilar and posterior cerebral arteries (0.3 to 0.7 mm outside diameter) were isolated from mongrel dogs which had been anesthetized with sodium pentobarbital (50 mg/kg, ip) and sacrificed by bleeding from common carotid arteries. The vessels were cut helically into strips and vertically fixed under a resting tension of 1.5 g in a muscle bath containing modified Ringer's solution. The upper end of the strip was connected to a force-displacement transducer. The bathing medium was gassed with a mixture of 95% O₂

FIG. 1. Typical recordings of the response of a basilar arterial strip to serotonin and 5-HIAA. Concentrations of serotonin, from 1 to 5; 10^{-9} , 5×10^{-9} , 2×10^{-8} , 10^{-7} and 5×10^{-7} M, respectively.

FIG. 2. Dose-response curves of serotonin and 5-HIAA (left) and dose-response curves of serotonin in the presence or absence of 5-HIAA (right). Vertical bars represent standard errors of means. For the right figure, contractions caused by 2×10^{-6} M serotonin in control media were taken as 100% (645 ± 103 mg, $N=6$). Numbers of preparations used: 5 for the left figure and 6 for the right.

and 5% CO₂ and was maintained at $37 \pm 0.5^\circ\text{C}$. Serotonin creatinine sulfate and 5-HIAA were added directly to the bathing medium in cumulative concentrations. Details of the methods were described in an earlier report (8).

In cerebral arterial strips, serotonin in concentrations in a range from 10^{-9} to 2×10^{-6} M caused a dose-dependent increase in the tension. In contrast, 5-HIAA in concentrations from 10^{-5} to 10^{-3} M elicited relaxation of these arteries in a dose-dependent manner (Fig. 1). Quantitative comparison of the response to serotonin and 5-HIAA obtained from the same arterial strips is presented in Fig. 2. The 5-HIAA-induced relaxation was more evident when the arteries had been contracted with prostaglandin F_{2a} (3×10^{-7} to 10^{-6} M). Relaxation induced by 5×10^{-5} M 5-HIAA was not inhibited by 5×10^{-6} M propranolol in 3 out of 3 strips, 10^{-6} M atropine in 2 out of 2 and 2×10^{-7} M ouabain in 2 out of 2. Thus, it appears that beta-adrenergic, cholinergic and electrogenic Na⁺ pump mechanisms are not involved in the genesis of the relaxation.

The dose-response relationship for serotonin was not altered when cerebral arterial strips were treated for 20 min with 2×10^{-4} M 5-HIAA (26 ± 18 mg relaxation, N=6) (Fig. 2 -right). In 2 preparations, further increase in the concentration of 5-HIAA to 10^{-3} M did not influence the contractile response to serotonin (Fig. 1).

Our study demonstrated that the deaminated metabolite of serotonin, 5-HIAA, showed neither serotonin-like nor anti-serotonin action on isolated canine cerebral arteries, while in contrast a metabolite of serotonin, 5-HK, of which the indole ring was opened possessed both serotonin-like and anti-serotonin actions (3).

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COMPARISON OF N-OXIDATION AND N-DEMETHYLATION OF DIMETHYLANILINE IN HUMAN LIVER

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A number of tertiary amine drugs have been demonstrated to undergo two main oxidative reactions by hepatic-microsomal enzymes requiring both NADPH and molecular oxygen. One is N-demethylation reaction which is catalyzed by cytochrome P-450, a