degree of contraction. This blocking effect of propranolol on the phenylephrine-induced contraction seemed to be non-specific, because the same concentration of propranolol also inhibited the contraction induced by serotonin. When dibenamine in the concentration of 2.5×10^{-7} g/ml was added to the bath 30 min before phenylephrine, both phases of relaxation (if present) and contraction were completely abolished.

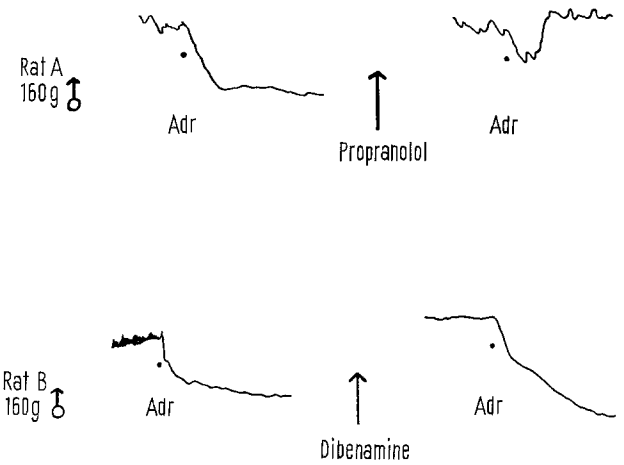

Fig. 2. Change in response to 5×10^{-8} g/ml of adrenaline (Adr) in the presence of 2.5×10^{-7} g/ml of propranolol (Rat A), and that in the presence of 2.5×10^{-7} g/ml of dibenamine (Rat B).

The foregoing results suggest that stimulation of α-receptors produces an initial relaxation followed by a secondary contraction in the rat jejunum, because this typical response can be seen by the addition of adrenaline in the presence of propranolol. Phenylephrine also produced similar response. The fact that this type of reaction to adrenaline, or to phenylephrine is almost completely abolished by the pretreatment of the jejunum with dibenamine, indicates that the response mentioned above is produced by stimulation of α-receptors. It is apparent that stimulation of β-receptors produces relaxation of the jejunum, because in our experiment isoproterenol produced relaxation, which was not inhibited by the pretreatment with dibenamine but was completely abolished by propranolol. So, the relaxation of the rat jejunum could be produced by stimulation of either α- or β-receptors. But the contraction could be produced by stimulation of α-receptors.

Zusammenfassung. Es wird gezeigt, dass die Stimulation der α-Rezeptoren am isolierten Rattenjejunum Erschlaffung und Kontraktion verursacht, während die Stimulation der β-Rezeptoren nur Erschlaffung bewirkt.

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Autoradiographic Localization of 5-Hydroxytryptamine in Monkey Pineal Gland

The pineal gland of man and other mammals contains a high concentration of 5-hydroxytryptamine (5-HT) and the highest levels recorded have been in the rat and monkey[1,2]. It appears[3] that the principal intrapineal pathway for the metabolism of 5-HT depends on the activity of the enzyme monoamine oxidase (MAO) which is present in large amounts in pineal gland tissue[4]. The present report deals with a morphological study of the monkey pineal gland employing an autoradiographic technique. The investigation is concerned with first, demonstrating in vivo uptake of tritium-labelled 5-hydroxytryptophan (^{3}H-5-HTP) and its localization within the gland, secondly, the conversion of ^{3}H-5-HTP to ^{3}H-5-HT and thirdly, detecting alterations in intrapineal levels of isotope following interference with MAO activity. Because the level of 5-HT in monkey pineal gland fluctuates over a 24 h period, being at its highest concentration during the daily light period[1], an appropriate time in the morning was chosen for the administration of the isotope.

Three healthy adult male cynomolgus monkeys, *Macaca irus*, housed at the Commonwealth Serum Laboratories, Melbourne, weighing 4000–5000 g each, were used. 2 animals were given 5 mCi/kg ^{3}H-5-HTP[5], specific activity 3.3 Ci/m*M*, at 11.00 h. Previously 1 of the animals received at 10.00 h 20 mg/kg tranylcypromine sulphate, a rapidly acting MAO inhibitor[6]. Both substances were administered by i.p. injection. Tissues from the third animal, which was not injected, were used as controls to exclude possible chemical artefacts in the nuclear emulsion of the autoradiographs. 2 h after the administration of ^{3}H-5-HTP the monkeys were exsanguinated under deep i.v. barbiturate anaesthesia and the pineal glands removed. After fixation in 10% (v/v) phosphate-buffered formol-saline, pH 7.0, the glands were dehydrated in ethanol, embedded in paraffin wax, cut serially at 4 μ thickness and mounted on acid-cleaned glass microscope slides. Sections were dewaxed, dipped in liquid nuclear emulsion (Ilford K5) diluted 1:4 with glass-distilled water and exposed for 10 weeks at 4 °C. The slides were developed for 4 min in Neutol-S (Agfa) diluted with water (1:7), fixed in 'Amfix' solution (May and Baker) for 3 min and then washed for 20 min in filtered tap water. The sections were stained with nuclear fast red and tartrazin O (Chroma) and mounted in polystyrene.

Precise localization of radioactivity was demonstrated over the pineal gland (Figure A). Very few silver grains were present over pinealocytes in the autoradiographs prepared from the monkey given ^{3}H-5-HTP alone (Figure B), but in those prepared from the animal given MAO inhibitor, in addition to ^{3}H-5-HTP, dense collections of grains had developed over these cells (Figure C).

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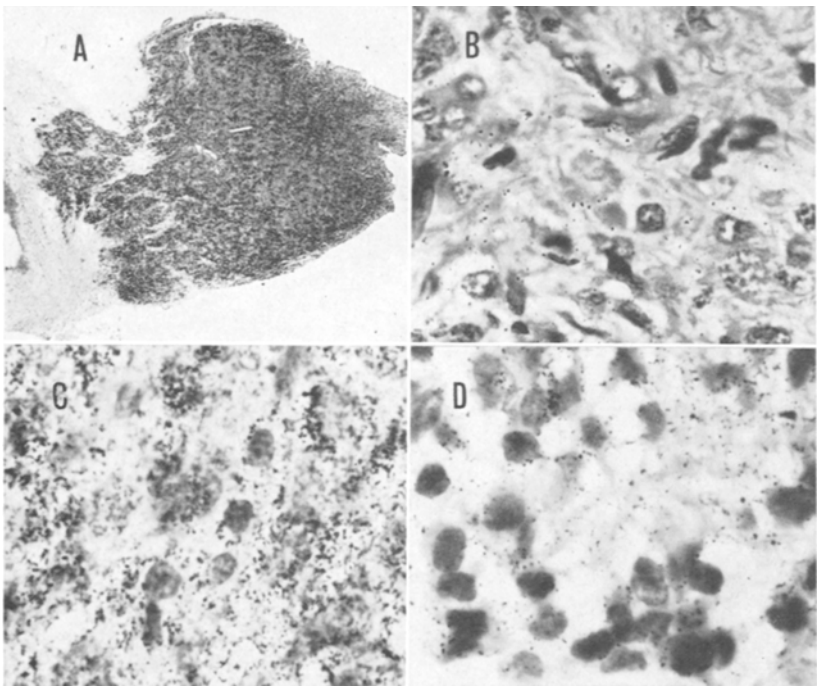
[6] Donated by Smith Kline and French Laboratories.



(A) Autoradiogram of section of pineal gland and adjacent brain tissue from cynomolgus monkey injected 25 mCi ^{3}H-5-HTP 60 min after administration of MAO inhibitor. It shows dense silver grain deposition precisely localized over gland tissue indicating presence of high concentration of isotope. Nuclear fast red and tartrazin (× 30). (B) Autoradiogram of section of pineal gland from cynomolgus monkey injected 25 mCi ^{3}H-5-HTP with no MAO inhibitor showing sparse silver grain deposition. Compare with (C) and (D). Nuclear fast red and tartrazin (× 350). (C) and (D) Autoradiograms of section of pineal gland from the same monkey as shown in (A) showing silver grain distribution concentrated mainly over cytoplasm and cytoplasmic processes. Nuclear fast red and tartrazin (× 300).

Grain counts per pinealocyte were 5 times greater in this animal than in the former and grain distribution was concentrated over the cytoplasm and cytoplasmic processes of the cell. There was minimal labelling over the nucleus (Figure D). In the autoradiographs prepared from the uninjected animal no evidence of chemical fogging of the emulsion was found.

Silver grain deposition over pinealocytes shows that these structures contain isotope. In the present study the sparseness of grains in the gland of the monkey not given MAO inhibitor indicates a low tissue concentration of isotope and implies that isotope is being removed. However, removal of any isotope from these cells by MAO depends on the conversion of ^{3}H-5-HTP to ^{3}H-5-HT by the enzyme aromatic L-amino acid decarboxylase[7] because ^{3}H-5-HTP is not a substrate for MAO[8]. Since the pineal gland contains the enzymes necessary to synthesize and destroy 5-HT[3,7], the low concentration of isotope in this animal is very likely due to the uninhibited breakdown of synthesized ^{3}H-5-HT by MAO. This hypothesis is supported by the demonstration of a high concentration of isotope in the animal in which MAO activity was inhibited. These findings are similar to those made earlier[9] on rat brain neurones in vivo and in tissue culture and are consistent with the known rapid turnover of 5-HT[10–12].

Zusammenfassung. Die Verteilung von aus 5-Hydroxy-Tryptophan entstandenem Serotonin in der Zirbeldrüse von Affen wird beschrieben.

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Comparison of β-Adrenergic Blocking Activity of DCI, H56/28, ICI50172, LB46, Methoxamine, MJ1999 and Propranolol in the Blood Perfused Canine Papillary Muscle Preparation

Since β-adrenergic blocking action of DCI[1] was found, many active compounds have been successively synthesized in the past decade. Qualitative differences, however, were found among different β-adrenergic receptors[2]. Previously we compared the relative potency of DCI, methoxamine, propranolol, MJ1999, H56/28, LB46 and ICI 50172 to block the positive chronotropic effect of isoproterenol which was given intra-arterially into the sinus node artery[3]. In this study we compared the potencies of these compounds to block the positive inotropic effect of norepinephrine using the blood perfused papillary muscle preparation of dogs.

The heart was removed from a dog, anesthetized with ether and plunged into the cold Tyrode's solution. The