MAO inhibitors would be of therapeutic value for enhancing antipsychotic activity and attenuating or controlling side-effects which may originate from the excessive formation and turnover of DA induced by antipsychotic drugs.

Zusammenfassung. Pargylin und Pheniprazin vermindern stark die Dopa-Anreicherung (erhöhte Dopamin-Synthesegeschwindigkeit) im corpus striatum der Ratte nach Trifluoperazin und Tetrabenazin. Dopamin-spezifische MAO-Hemmer könnten deshalb therapeutischen Wert haben in der Kontrolle von tardiver Dyskinesia, die möglicherweise durch erhöhte Bildung und Umsatz von Dopamin unter dem Einfluss von anti-psychotischen Drogen hervorgerufen wird.

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Increased Vascular Permeability Induced in Synovialis of the Rat by Histamine, Serotonin and Bradykinin

Histamine, serotonin and bradykinin evoke increased vascular permeability when injected into some but not all mammalian tissues. In the rat, histamine induces a permeability response in skin, subcutaneous tissue, skeletal muscle, pleura and peritoneum, but not in testis, kidney or brain[1]. No studies of the effect of histamine, serotonin or bradykinin on the vascular permeability of synovialis of the rat have been reported, although histamine is known to increase the vascular permeability of synovialis in the monkey[2] and rabbit[3]. Further, the relative increase in vascular permeability induced by the above substances has been studied mainly in the skin of various laboratory animals[4] and little is known of their corresponding effects in other tissues.

This paper reports an investigation of the relative effects of histamine, serotonin and bradykinin on the vascular permeability of the synovial membrane in the stifle joint of the rat, and an electron microscopic study of synovial vessels rendered abnormally permeable by these substances.

Materials and methods. Albino rats of both sexes (body weight 250–350 g) were used, being lightly anaesthetized with ether for all injections. Serial 10-fold dilutions of histamine acid phosphate (0.36–360 µg histamine base/ml), serotonin creatinine sulphate (0.005–50 µg serotonin base/ml) and bradykinin (0.01–10 µg/ml) were prepared in Tyrode solution, pH 7.3; 0.05 ml of each dilution of each substance was injected into both the left and right stifle joints of 5 rats. The stifle joints of a further 5 rats, injected with 0.05 ml Tyrode solution alone, served as controls.

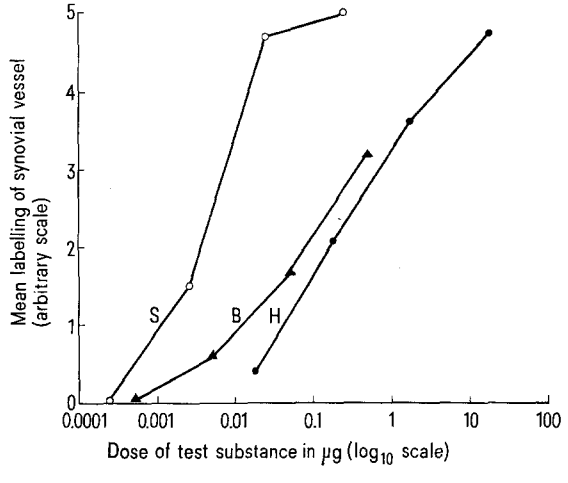

Fig. 1. Increased vascular permeability (assessed by carbon labelling of synovial vessels) induced in rat's synovialis by serotonin (S), bradykinin (B) and histamine (H). The mean score of the control-stratum synoviale was 0.25.

Increased vascular permeability induced in the synovialis was detected by injecting each animal i.v. with colloidal carbon (Gunther Wagner, C11/1431a, Pelikan, Hanover), 0.1 ml/100 g body weight, just prior to injection of the joints with the above substances. Circulating colloidal carbon is removed from the blood by the reticulo-endothelial system within 1 h, but during that period, carbon also collects in the walls of abnormally permeable blood vessels[5]. 75 min after the i.v. injection of colloidal carbon, each animal was killed and the stifle joints were opened to expose the synovialis. The synovial membranes were fixed in formaldehyde, 'cleared' in glycerol and examined with a dissecting microscope. The amount of carbon deposited in the walls of the synovial vessels (referred to as 'labelling' of the vessels) of each joint served as an index of the increased vascular permeability and was scored on an arbitrary scale 0 to 5. 16 of the 150 joints in the series contained blood at dissection and were excluded from the results as haemorrhage into the joint cavity is known to increase the permeability of the synovial microvasculature[6].

Synovial membranes were prepared for electron microscopy following intra-articular injection of 1.8 µg histamine base, 0.25 µg serotonin base and 0.5 µg bradykinin, respectively. The animals were killed 8 min after giving i.v. colloidal carbon and injection of the joints with each substance: the synovial membranes were removed and fixed in combined aldehyde fixative[7] and osmium tetroxide. Epon embedded sections were stained with uranyl acetate and lead citrate, and examined with a Philips 300 electron microscope.

Results and discussion. Histamine, serotonin and bradykinin each increased the vascular permeability of synovialis in the range of doses tested (Figure 1). Histamine had least potency, the minimum dose required to induce labelling of synovial vessels being 0.018 µg per joint. Maximal labelling of synovial vessels was obtained with a dose of 18 µg histamine per joint. Serotonin had

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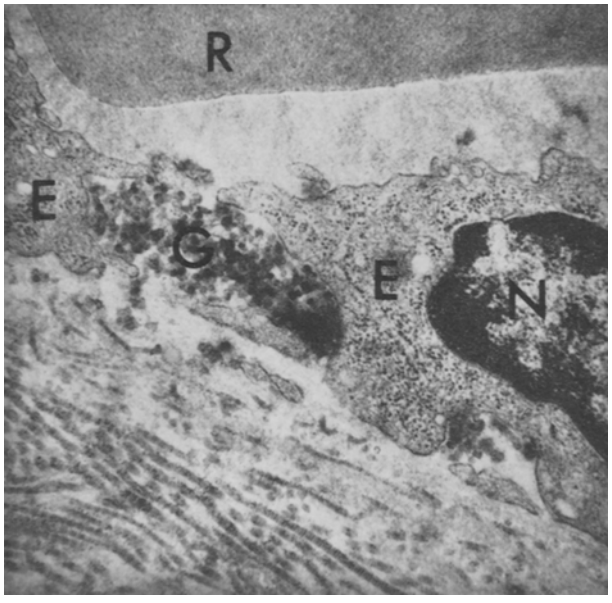

Fig. 2. Electron micrograph of synovial venule following intra-articular injection of serotonin. Carbon particles have accumulated in a gap (G) between 2 endothelial cells (E, E); R, erythrocyte in lumen; N, nucleus of endothelial cell. × 20.000.

approximately 70 times greater potency than histamine, maximal labelling of vessels being obtained by a dose of 0.25 µg. The synovial membranes of joints injected with 2.5 µg serotonin exhibited a similar amount of vascular labelling as those of joints injected with 0.25 µg, but labelling of vessels also occurred in muscle tissue adjacent to the joints. Bradykinin had approximately twice the potency of histamine in a dose range of 0.005 to 0.5 µg per joint. Maximal labelling of synovial vessels was not obtained with the highest test dose of bradykinin.

The relative potency of histamine, serotonin and bradykinin on the vascular permeability of synovialis therefore approximates the relative potency reported for these substances in rat's skin[4].

Electron microscopic examination of synovial vessels obtained from joints 8 min after intra-articular injection of histamine, serotonin or bradykinin revealed changes for each substance similar to those described for cremaster muscle of the rat[8]. Carbon particles were found beneath, and in gaps between, the endothelial cells of venules (Figure 2). Carbon deposits were not found in the walls of capillaries with either continuous or fenestrated endothelium[9]. In labelled venules, the nuclei of endothelial cells frequently showed prominent indentations of the nuclear membrane, a change which has been interpreted as resulting from contraction of the cytoplasm of the endothelial cell[10].

The above results indicate that in the rat, histamine, serotonin and bradykinin induce increased vascular permeability in the synovialis, that the mechanism of action of these substances is the same in synovialis as in skin and muscle, and that the relative potency of these substances is similar in synovialis and skin.

Résumé. La perméabilité vasculaire de la membrane synoviale du rat est augmentée par l'histamine, la sérotonine et la bradykinine. Dans cette réaction la sérotonine est plus active que l'histamine et la bradykinine.

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Increased Catecholamine Excretion in the Rat After Administration of α-Methyl-Tyrosine

Alpha-methyl-*para*-tyrosine (α-MpT), an analogue of tyrosine, has been shown to inhibit tyrosine-hydroxylase competitively, in vitro[1] as in vivo[2]. Thus this drug has been widely used as an inhibitor of norepinephrine (NE) synthesis in various experimental conditions, mainly for the estimation of both the rate of synthesis and the tissular turnover of NE in the rat[3–5]. As a matter of fact, injection of α-MpT to guinea-pigs or rats has been found to decrease the tissue levels of NE[2,3]. Furthermore, because of its inhibitory effect on catecholamine production, α-MpT has also been used clinically, especially for the treatment of amine producing tumors[6].

As far as we know, no study has been devoted, however, to the possible effect of α-MpT on both the excretion and the oxidation of catecholamines. The purpose of the present work was to test this hypothesis by determining the effects of α-MpT on the urinary excretion of both epinephrine (E) and NE as well as of their metabolite 3-methoxy-4-hydroxy-mandelic acid (VMA) in normal rats. The effects of this drug on NE excretion were also studied in adrenalectomized rats.

Materials and methods. Male Wistar rats, weighing 180–200 g and fed on stock laboratory diet, were injected i.p. with a single dose (100 or 200 mg/kg) of either α-MpT (Merck, Sharp and Dohme Research Laboratories, Rahway, N.J.), as a 0.5 *M* phosphate buffer solution (20 mg/ml), or α-MpT methyl ester (compound H 44/68,

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