The Effect of Bradykinin on Permeability of Skin Blood Vessels

The ability of i.c. administered bradykinin to enhance the permeability of skin vessels has been established by several investigators[1-7]. Studies of the effect of kinins on blood vessels is of significance for understanding the pathogenesis of inflammation. Therefore we investigated the comparative sensitivity of skin vessels to bradykinin and histamine, duration of their action, tachyphylaxis and the possibility of summation of these factors' action on vessel permeability.

Materials and methods. Experiments were made on 60 6-month-old (2.7–3.3 kg) and 3-month-old (2.1–2.7 kg) male rabbits, 36 male Wistar rats (350–420 g) and 50 guinea-pigs (350–520 g). Freshly prepared solutions (0.1 ml) of synthetic bradykinin[8] and histaminehydrochloride (Pharmaceutical Works, Riga, USSR, and G. Lowson, England) in saline were injected i.c. into previously shaved parts of the animal's abdomen. The increase in blood vessel permeability was controlled with i.v. administered Evans blue (20 mg/kg).

The appearance of blue patches on the skin more than 7 mm in diameter 10 min after i.c. administration of these solutions was taken as evidence of blood vessel permeability derangement.

Results. The results were evaluated according to the method of LITCHFIELD and WILCOXON as modified by ROTH[9].

The comparative sensitivity of skin vessels to bradykinin and histamine was studied in experiments on rabbits, guinea-pigs and rats. Different amounts of bradykinin (from 1×10^{-12} to 5×10^{-7} g) and histamine (from 5×10^{-7} to 1×10^{-4} g) were injected i.c. into symmetrical parts of abdominal skin. Five min later Evans blue was given i.v. The results are summarized in Figures 1 and 2.

Bradykinin administration led to derangement of blood vessel permeability in 50% of the cases (ED_{50}) in guinea-pigs, adult rabbits and rats at dosages of 7×10^{-13}, 1×10^{-12} and 4×10^{-9} g respectively. ED_{50} for histamine in guinea-pigs, rabbits and rats proved to be 2×10^{-8}, 1.6×10^{-8} and 2.2×10^{-7} g respectively. This shows that skin vessels of guinea-pigs, rabbits and rats are 30,900, 14,000 and 56 times more sensitive to bradykinin than to histamine in terms of weight, and 290,000, 132,000 and 520 times on a molar basis.

Skin blood vessels of young rabbits (3 months old) were found to be less sensitive to bradykinin and histamine than the vessels of adults. In most of the young rabbits, the disturbances of blood vessel permeability appeared only after injections of 1×10^{-9} g bradykinin and 3×10^{-7} g of histamine.

To determine the duration of bradykinin effect on the blood vessel permeability, the solutions studied were injected i.c. at definite time intervals. After the last bradykinin injection, a solution of Evans blue was administered i.v. We found that the disturbances caused by bradykinin do not last long in spite of its high activity. The enhancement of rabbit and guinea-pig blood vessel permeability after 1×10^{-8} g bradykinin injection was maintained for 7–8 min. If the dose of bradykinin was increased by a factor of 50, the permeability increase was only prolonged to 10–11 min in rabbits and to 8–9 min in guinea-pigs. In experiments on rats, the injection of 5×10^{-7} g of bradykinin led to an increased blood vessel permeability of 3–4 min duration. The histamine effect on blood vessel permeability lasted longer. After i.c. injections of histamine in doses of 1×10^{-6} and 1×10^{-5} g, the increase of permeability was observed for 20 and 30 min.

Special experiments were made to study the ability of blood vessels to react to repeated injections of bradykinin and histamine. 1×10^{-8} g of bradykinin in 0.05 ml of saline was introduced every 30 min during 1 h into the corners of a square (2.5 × 2.5 cm) of rabbit abdominal skin. The same experiments were made with histamine introduced in doses of 1×10^{-6}, 1×10^{-5} and 1×10^{-4} g every 20 min for a period of 1 h. Solutions of Evans blue were injected i.v. after 20, 30, 40 and 60 min. In these experiments, the repeated injections of bradykinin caused an increase in blood vessel permeability in all cases. In contrast to these results, the disturbances of permeability in experiments with histamine were observed only in the first 30 min.

Bradykinin and histamine as 2 natural permeability factors may act on the vessels simultaneously. Therefore the concerted effect of bradykinin and histamine was studied

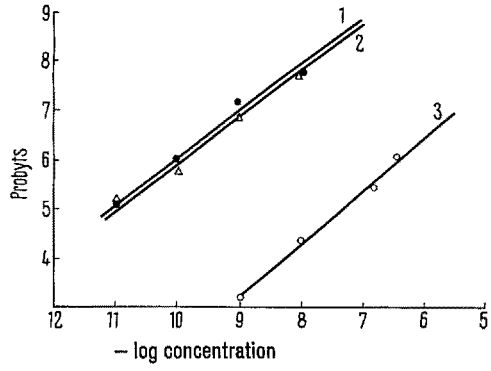

Fig. 1. Effects of bradykinin on the skin blood vessel permeability of guinea-pigs (1), rabbits (2) and rats (3).

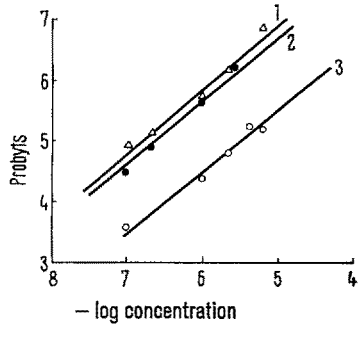

Fig. 2. Effects of histamine on the skin blood vessel permeability of rabbits (1), guinea-pigs (2) and rats (3).

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in experiments on 6 rabbits. We determined the sensitivity of the animals to both substances previously. Then we used amounts of bradykinin and histamine which do not disturb the blood vessel permeability, mixed them, and injected them i.c. The summation of effects of both mediators was observed in these experiments (Figure 3).

Discussion. The investigations confirmed the high sensitivity of skin blood vessel permeability of rabbits, guinea-pigs and rats to bradykinin[5,6]. More pronounced differences between the sensitivity of blood vessels to bradykinin and histamine found in our experiments are probably explained by the fact that we have taken for calculation the derangement of permeability appearing in 50% of the animals. The blood vessel permeability derangement of short duration observed after the injections of bradykinin is in accordance with published data[10]. This mode of action of bradykinin appears to depend on high activity of the skin kininase. But our data do not rule out the possibility of the participation of kinin in the pathogenesis of inflammation where the conditions for continuous formation of kinins may exist. Lower sensitivity of vessels to histamine than to bradykinin and small taxyphylaxis to bradykinin are serious arguments favouring bradykinin as mediator of inflammation.

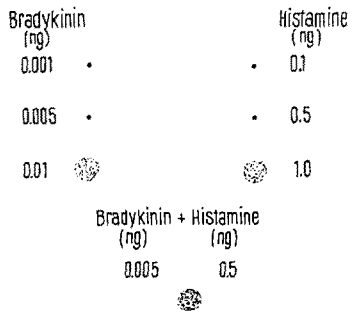

Fig. 3. Simultaneous actions of bradykinin and histamine on skin blood vessel permeability of rabbits.

The observed summation of the effects of bradykinin and histamine on blood vessel permeability appears to play an important role in the first phase of inflammation where histamine is considered to be the main mediator[11].

Zusammenfassung. Es werden quantitative Vergleiche in 3 Spezies der Hautgefäss-Empfindlichkeit gegenüber Bradykinin und Histamin angestellt.

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Does Acute Obstruction of the Common Bile Duct Produce Distension of the Rat Bile Tree?

During short periods of obstruction of the common bile duct in rats biliary secretion apparently continues[1]. This leads to a rising intrabiliary pressure which is ultimately stabilized by biliary leakage (regurgitation). Sudden release of obstruction at this time is immediately followed by a gush of bile which may be recorded with a biliary cannula and drop counter. The increased flow rate subsides to the basal rate in a few minutes.

It is generally accepted that the bile tree distends in response to increased pressure resulting from acute obstruction, and that the gush of bile seen on release of obstruction is due to the rapid ejection of stored bile produced by the elastic recoil of the distended bile tree. However, the suggestion has been put forward that in order to continue secreting against a raised pressure the hepatic cells must accumulate extra substrate (i.e. accumulate substances which drive the secretory mechanism)[2]. Release of acute obstruction would be expected to produce an increased secretory rate during the unloading of the excess substrate. This increased secretory rate could be wholly or partly responsible for the temporary increase in flow rate observed on release of obstruction.

The cause of this increased flow rate is of some importance in the measurement of the distended capacity of the bile tree by the dye method described elsewhere[3]. This method measures the volume of bile present in the tree (= capacity of bile tree) at the time of injection of a marker dye. The dye is injected i.v. and since its appearance in the collected bile is taken to indicate the arrival of bile secreted after the injection time, it follows that secretion of bile in the time period between dye injection and dye secretion represents an error of the method resulting in over-reading of true capacity. With normal bile flow rates in rats this error is probably small[3] but could be significantly large if the secretion rate approximated to the bile flow rate seen at the time of release of obstruction.

The distensibility of the bile tree is important in other studies too, as, for example, in recent investigations on the dual origin of bile in dogs[4].

One approach to this problem is to measure the bile tree capacity at raised intrabiliary pressures under conditions allowing substrate unloading, and to compare the results with measurements made at the same pressure and with the same animal but arranging matters so that substrate unloading cannot occur.

In the first experiment the cannula exit was kept at the level of the hilum of the liver and a side arm was attached to an adjustable constant level device which was set at the desired height. The cannula exit was obstructed

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