## The Kinin Content of Human Blood at Rest and During Vasodilatation

Certain biologically active peptides released from plasma proteins under particular conditions have been collectively designated the plasma kinins. They stimulate smooth muscle, produce vasomotor changes and increase capillary permeability.

Kallidin and bradykinin are vasodilator kinins released from the same plasma substrate[1]. Bradykinin is a nonapeptide and kallidin a decapeptide having an additional lysyl residue at the N terminal end of the molecule. Both kinins have a strong vasodilator and hypotensive action.

Because of their outstanding biological effects and their occurrence in the body, plasma kinins are believed to participate in various physiological mechanisms such as vasodilatation. HILTON and LEWIS[2-5] have presented evidence that kinin-forming enzymes are released from the submaxillary gland and from the tongue of the cat when vasodilatation was induced by stimulation of the chorda tympani nerve. Similar results were obtained by HILTON and JONES[6] on the perfused cat pancreas when the vasodilatation was produced by acetylcholine or by pancreazymin.

According to FOX and HILTON[7], kinins are released from the human forearm when sweating and thermal vasodilatation is induced, and ROCHA E SILVA and ANTONIO[8], by heating the rat's leg to 44–45°C, found a rise of the kinin content of the fluid perfusing the subcutaneous tissue. On the other hand, muscle vasodilatation that follows stimulation of the motor nerve does not appear to be mediated by kinin release[5].

All the above-mentioned experiments were carried out using electrolyte solutions as the perfusing fluid. We decided to investigate the kinin content of the venous blood of the human forearm during vasodilatation produced by heating or by exercise.

*Material and methods.* Normal male subjects, 17 to 30 years old, were used in the experiments. Venous blood was obtained from the antecubital vein with a 1 mm bore needle and from the femoral artery with a 0.8 mm bore needle. Blood was immediately precipitated with 4 Vol of 96% alcohol. The immediate precipitation of the blood is very important to avoid any extravascular formation or destruction of the plasma kinins.

Kinins were estimated by the method of BINIA et al.[9], which detects levels as low as 0.1 mcg of bradykinin per 100 ml of blood.

Thermal vasodilatation was produced by immersion of the hand and lower forearm in warm water (between 40 and 45°C) for 10 min.

Muscular work was undertaken in a Mosso ergograph employing four fingers and a weight of 2–4 kg. The fingers were flexed at a variable rate and the exercise stopped when the subject was unable to proceed on account of fatigue. This always happened between 10 and 20 min after the beginning of the exercise when the total work done ranged between 20 and 80 mkg.

*Results.* Kinin content of arterial and venous blood of resting subjects: In 25 normal subjects kept under basal conditions the kinin content of the venous blood was estimated. Values ranged from 0 to 4.0 U of bradykinin per 100 ml of blood with an average of 1.2 U (Figure 1).

Simultaneous determinations of the kinin content of the arterial and the venous blood were carried out in 8 subjects. Figure 1 shows that there are no significant differences in the kinin content of arterial and venous blood. In one venous sample a very high value (20 U/100 ml) was found.

Kinin content of venous blood in exercise and thermal vasodilatation: In four subjects the kinin content of the blood from the antecubital vein was estimated immediately before and 10 min after immersing the hand in hot water at 40–45°C and, thirdly, 20 min after withdrawal from the bath. Figure 2 shows that there are no significant differences between any of the 3 samples.

Similar determinations were carried out in seven subjects before the exercise, immediately after, and 15–25 min afterwards. No difference was found between the samples collected before and those collected after exercise (Figure 2).

*Discussion.* Kinin-forming enzymes have not been found in muscular tissues, but the plasma system could be activated in some way by muscle or other tissue. If that should be the case, kinins formed within the capillaries could produce local vasodilatation and hyperaemia. Although kinins are rapidly destroyed by blood, some increase in the level of kinin in the venous effluent was ex-

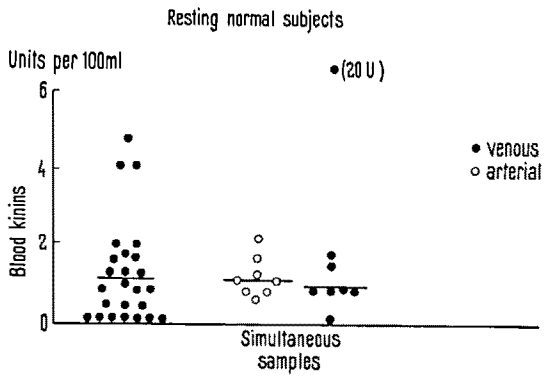


Fig. 1. Kinin content of the blood of normal subjects. All subjects under basal conditions. The averages are about 1 U/100 ml of blood, which corresponds to 0.1 mcg of bradykinin per 100 ml. Blood from the femoral artery and antecubital veins.

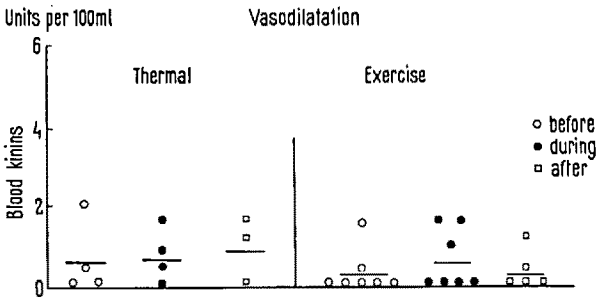


Fig. 2. Kinin content of the venous blood during vasodilatation of the forearm. Blood was taken from the antecubital veins.

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pected to occur. In fact, the average circulation time between capillaries in the hand and forearm and the veins in the antecubital fossa is probably well below 15 sec. The half-life of bradykinin in the circulation has been calculated to be some 30 sec[10]; so most of the kinin which is formed in the capillaries should still be found in the venous blood. If kinin should be formed in the extravascular space, where the plasma substrate comes in contact with the cells, as suggested by LEWIS[11], the amount which reaches the larger venous trunks would be smaller.

Kinins appear to have a role in vasodilatation occurring within the pancreas and the salivary gland[2,3,6], but even in those cases where the evidence seems strongest, there are some doubts. For instance, SCHACHTER[12] has shown that in the guinea-pig, salivary kallikrein will not form kinins with its own plasma.

The above results show that kinins are found in the circulating blood of normal individuals. The levels are low, 1 U/100 ml of blood (0.1 mcg bradykinin), and near the limit of sensitivity of the method employed, but high enough to have physiological implications. Since the kinin content of the arterial blood is comparable to the venous, plasma kinins appear to be formed within the circulating blood[13].

*Résumé.* Le contenu en «kinines» du sang veineux ou artériel humain équivaut à 0.1 mcg de bradykinine par 100 ml. Le contenu des veines du pli du coude n'augmente pas pendant la vasodilatation thermique ni pendant le travail des muscles de l'avant-bras.

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## DNA Synthesis in Glial Cells during Nerve Regeneration

In a series of experiments HYDÉN et al. have demonstrated that the metabolic processes in the nerve cell and the surrounding glial cells are interrelated[1]. During nerve regeneration the total amount of proteins and ribonucleic acid per nerve cell increases[2]. Tracer studies have shown an increased incorporation of lysine[3,4] and of orotic acid[3] per nerve cell in regenerating hypoglossal neurons. The present study demonstrates that changes also occur in the surrounding glial cells during nerve regeneration.

The glial cells surrounding the neurons belonging to the hypoglossal nucleus in rabbits weighing 1.5–1.6 kg were studied. The hypoglossal nerve on the right side was crushed with cooled forceps, where it intersects the *musculus digastricus*. Before the experimental procedure was carried out, a cannula was implated with its tip in the *cisterna magna* according to a technique described by KOELLE and KOENIG[5]. Through this cannula radioactive precursors were injected intracisternally. The DNA synthesis in the glial cells during nerve regeneration was studied with $H^3$-thymidine by autoradiography. Each rabbit received a total of 200 $\mu$c $H^3$-thymidine (Schwarz lab., sp. act. 3.0 C/m*M*) divided into four equal doses 24, 22, 20 and 18 h before sacrifice at 9 p. m. Carnoy fixed sections through the *nucleus hypoglossus* in the *medulla oblongata* were extracted with 0.2 *N* perchloric acid at 4°C for 5 min and then thoroughly rinsed in water before coating with the autoradiographic emulsion (Ilford, K2) according to a slightly modified technique described by KOPRIWA and LEBLOND[6]. Some slides from each animal were incubated with deoxyribonuclease according to EDSTRÖM et al.[7] before coating with the emulsion. After exposure for eleven days the autoradiographs were developed and stained through the emulsion with toluidine blue at 4.0 and mounted. The number of glial nuclei with more than four grains over the nucleus was calculated in the same region of *nucleus hypoglossus* at different postoperative intervals (Table I).

*Results.* During the second to the sixth postoperative day there is an intensive DNA synthesis in the glial cell population on the regenerating side compared to the unoperated side. On the third postoperative day around 10% of all glial cells in the regenerating nucleus are labelled. In all animals one or less than one labelled glial nucleus is

Table I. The number of $H^3$-thymidine labelled glial nuclei per section on the regenerating and control side of *nucleus hypoglossus*. Rabbits were injected intracisternally four times: 24, 22, 20, and 18 h before sacrifice

| Days after operation | 1 | 2 | 3 | 6 |
|---|---|---|---|---|
| Regenerating side | 2.2 | 9.6 | 22.3 | 8.7 |
| Control side | 1.0 | 0.6 | 0.1 | 0.1 |

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