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STUDIES ON BLOOD BRADYKININ IN MAN

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by

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GENERAL SUMMARY

PART 1 presents a historical survey of the advances in the elucidation of the plasma kinin system, including the isolation and synthesis of the important members of this group of polypeptides. A review is presented of the accumulating evidence for the possible participation of these substances in normal and disease processes.

PART 2 describes a method for the estimation of peripheral blood bradykinin levels, using a method of extraction and biological assay. With this it is possible to measure levels in the blood of all normal subjects so far examined. The average bradykinin level in brachial arterial blood is found to be 0.25 ng/ml ($\pm$ 0.23 ng/ml). These levels are lower than others reported but the average recovery of internal standard of 97% suggests that these figures are not low due to losses in the procedure.

In PART 3 attempts are made to relate blood bradykinin levels to peripheral circulatory changes. Direct heating of the hand causes the expected increase in blood flow and results in an increase in bradykinin levels in the venous blood draining that

part by up to 53%. In reactive hyperaemia and cold vasodilatation a fall in the venous bradykinin level is observed. It is shown that there is an arterio-venous difference in bradykinin levels across an extremity such as the hand,with arterial levels usually higher than the venous. The occasional observation of higher venous levels and the results of venous bradykinin assays during intra brachial artery bradykinin infusions, suggests that peripheral sites are able to produce bradykinin. It is also noted in this section that a generalised sympathetic discharge causes a lowering of endogenous arterial bradykinin levels, whereas sympathetic blockade produces an increase. The falling blood bradykinin levels observed in cold vasodilatation and reactive hyperaemia could be related to the painful nature of experiments and the resultant sympathetic nervous system overactivity.

In PART 4 it is shown that infusions of adrenaline result in falls of blood bradykinin levels and this seems to be achieved by an acceleration of the destruction of the peptide by kininase. Since the adrenergic blocking agent phenoxybenzamine can block this enzyme activation, the possibility is discussed that catecholamines act on a circulating " receptor " which can be blocked by small concentrations (10^{-7} M) of a specific adrenergic blocking agent. Conclusions are drawn that catecholamines are powerful modulators of kininase activity and may be responsible for settingthe half-life of bradykinin in blood (and in interstitial

fluid) within the large range encountered in normal blood viz. 3 sec $\geq t_{\frac{1}{2}} <$ 40 sec , and thus regulating the activity of bradykinin in regions where it is possibly acting as a physiological (or pathological) agent.

In PART 5 the flushing and other cardiovascular changes in the carcinoid syndrome, which have been related to the appearance of large amounts of bradykinin in the hepatic vein blood by other workers, are here related more directly with bradykinin changes in the peripheral circulation. The carcinoid blood bradykinin levels are evaluated in terms of levels found in normal people and a comparison is drawn between the effects of intravenous adrenaline infusions in normal and carcinoid syndrome subjects.

A small group of patients with cirrhosis and another of menopausal women, suffering from severe flushing attacks , have been studied to determine whether bradykinin was involved in their abnormal vascular manifestations. Using this present method , no direct evidence of this could be obtained, but interesting facets of these conditions , and the experimental findings are discussed that suggest that a more refined or differently directed approach may yet implicate the plasma kinins.