cursor in the biosynthesis of adrenocorticotrophic hormone.

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Spontaneous Plasma Kinin Formation in Human Plasma collected during Labour

Deficiency of substrate for induced plasma kinin production in the stored plasmas collected from women at the time of delivery has been shown[1]. This substrate deficiency was not observed in normal plasma (that is, from non-parturient individuals) stored for long periods at −20° C., or in plasma collected at time of delivery from women undergoing Cæsarean section at term before the onset of labour.

In the present series of experiments the plasmas were collected as previously described[1]; but, as soon as possible after their collection (5–25 min.), plasma aliquots were placed in polythene containers at 0° C. and tested forthwith, in doses of 0·1–0·01 ml., on the isolated rat uterus in a 10 ml. bath. It was then found that plasmas collected from women in labour showed marked oxytocic activity, which increased further for ½–1½ hr. This unusual activity was observed a short time before the onset of labour. The rapidity of its development increased throughout the first and second stages reaching, at its maximum, an activity equivalent to several units of oxytocin ('Syntocinon', Sandoz) per ml. plasma. It then declined, but was demonstrable for a variable period (usually 1–4 hr.) after completion of the third stage. These findings are in contradistinction to the negligible oxytocic activity which develops in normal plasma kept in polythene containers at 0° C. for 1 hr.[2].

The spontaneously produced oxytocic activity in parturition plasmas kept at 0° C. resembled that due to plasma kinin[3]. It rapidly disappeared when the temperature of the plasma was raised to 20° C. Conversely, the rate of disappearance of kinin added to plasma was markedly reduced when the plasma temperature was lowered from 20° C. to 0° C. This can be explained by the influence of temperature on plasma kininase. Since we have found the same kininase activity in normal and parturition plasmas, we consider that the rapidly developing oxytocic power of the latter, at 0° C., was almost certainly due to abnormally rapid formation.

The amount of spontaneous kinin formation in plasma samples collected at different stages of parturition was directly correlated with the degree of substrate depletion measured at these different stages[1].

We think it unlikely that plasmin was the enzyme responsible for the spontaneous production of oxytocic activity since the peak period for development of the latter in the plasma, and the subsequent depletion of kininogen, corresponds with the nadir of fibrinolytic activity reported in pregnancy plasma[4]. Moreover, normal plasma with high fibrinolytic activity (for example, after severe exercise or surgical operations) failed to develop a similar marked oxytocic activity. In addition, agents such as heparin (25 I.U./ml.) and ε-amino caproic acid (0·12 *M*), which inhibit plasmin, promoted the spontaneous kinin formation. These substances also potentiate kinin formation in normal plasma when it is exposed to glass, and this is known to be independent of the plasminogen–plasmin system[5,6].

The active oxytocic principle did not develop in parturition plasma to which the soya bean trypsin inhibitor (2 mgm./ml.) had been added. Like plasma kinin, it was extractable in boiling ethanol from active (that is, oxytocic) plasma kept at 0° C., but not from control samples of the same plasma kept at room temperature, and the activity of the extracts was rapidly destroyed by a crude amino-peptidase (*E. coli*) preparation. It is our opinion that it is probably a polypeptide.

The oxytocic activity in plasma or extract, unlike oxytocin, was not rapidly destroyed by sodium thioglycollate, though the build-up of kinin in parturition plasma kept at 0° C. was inhibited by this agent. In these respects the spontaneous kinin production resembled that of kinin formed by exposure of human plasma to glass, and, to a certain extent, the formation of bradykinin by trypsin added to human pre-active plasma. Differences in dose–response relationships between the spontaneously arising kinin of parturition plasma and oxytocin, and the marked lack of tachyphylactic response of the uterus towards the former, also suggest that we were not dealing with oxytocin itself.

The increasing rapidity of development of the parturition kinin throughout labour, reaching its maximum at the end of the second stage, suggests that the oxytocic activity may be related to the increasingly powerful contractions observed in the human uterus up to this time. The source of the active enzyme producing this oxytocic activity is not at present known.

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