Brain kinins and fever induced by bacterial pyrogens in rabbits

Bradykinin-like substances were reported to be present in cerebral tissue, together with enzymes required for their liberation and catabolism (Hori, 1968; Camargo & Graeff, 1969; Camargo, Ramalho-Pinto & Greene, 1972; Pela, Coelho & Rocha e Silva, 1972). Furthermore, intracerebroventricular injection of bradykinin in rabbits, cats and rats causes behavioural and somatic changes (Capek, 1963; Graeff, Pela & Rocha e Silva, 1969; Correa & Graeff, 1974).

Pela & others (1972) extracted kinin-like material from rabbit brain (not cortex or cerebellum) by precipitating cerebral proteins with 15% trichloroacetic acid, incubation with trypsin, dialysis and lyophilization. This activity, assayed biologically, was equivalent to 3 μg bradykinin g^{-1} of wet brain tissue.

In the present work using the same methods, we observed that the brain kinin-like activity in the rabbits was almost exlusively localized in the hypothalamus and very low in the brain stem. The data reported here are the means of eight results obtained from eight different samples.

The amounts were 4·0 $\pm$ 1·2 (s.e.m.) and 0·040 $\pm$ 0·003 μg bradykinin equivalents per g wet weight. Since pyrogens induce a biphasic response in rabbits (reviewed by Lechat & Gardey-Levassort, 1973), we killed the rabbits at the peaks occurring at 1·5 and 3·5 h after injection of *Escherichia coli* lipopolysaccharide (1·5 μg kg^{-1}, i.v.). At the first peak of fever, the kinin-like activity was 70% $\pm$ 10 of the control values, and at the second peak this activity was only 4% $\pm$ 2 (Fig. 1).

The kininogen-kinin system might therefore be involved in the pyrogen fever response in rabbits. Prostaglandins (PGs) of the E series seem likely to play an important role in pyrogen fever induction (Milton & Wendlandt, 1970; Feldberg, Gupta & others, 1972; Feldberg & Gupta, 1973), and there is evidence that bradykinin releases PGs (McGiff, 1974; Ryan & Ryan, 1974). Moreover, the PGE compounds can potentiate effects of bradykinin in some conditions (Ferreira, Moncada & Vane, 1973; Thomas & West, 1973), and it seems that PG's could act as modulators of bradykinin responses (Thomas & West, 1973; McGiff, 1974). A possible interaction of kininogenkinin system with PG's during bacterial pyrogen fever in rabbits remains to be investigated.

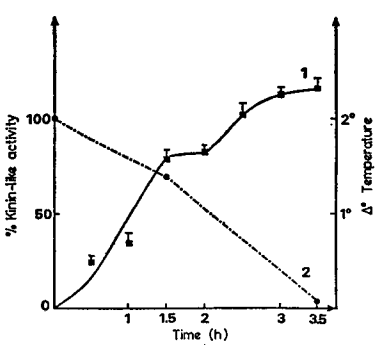

FIG. 1. Effect of *E. coli* lipopolysaccharide-induced fever (1·5 μg kg^{-1}, i.v.) (curve 1) on the hypothalamus kinin-like activity referred to bradykinin activity (curve 2) at the two peaks of fever in rabbits.

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A protective action of an anti-inflammatory steroid on collagen synthesis in rat carrageenan granuloma *in vitro*

Administration of anti-inflammatory steroids *in vivo* has been repeatedly shown to inhibit protein syntheses in experimentally inflamed tissues (Robertson & Sanborn, 1958; Bavetta, Bekhor & others, 1962; Bavetta & Nimni, 1964; Mikkonen, Lampiaho & Kulonen, 1966; Oronsky & Nocenti, 1967; Fukuhara & Tsurufuji, 1969; Nakagawa, Fukukara & Tsurufuji, 1971). In the present study, the effect of an anti-inflammatory steroid on the synthesis of collagen and non-collagen protein was investigated *in vitro* by incubating minced carrageenan granuloma in a medium containing the steroid.

A granuloma pouch was induced in male rats of the Donryu strain, 110–140 g, by injecting (s.c.) a 2% solution of Seakem 202 carrageenan according to Fukuhara & Tsurufuji (1969). On day 8 after carrageenan injection, granulation tissue was taken immediately after death and minced into 1–2 mm pieces 3 g of which was incubated with or without betamethasone disodium phosphate at 37° under an atmosphere 5% CO_2 in oxygen in 10 ml of Krebs saline serum substitute (Krebs, 1950) containing 10 mg each of potassium penicillin G and dihydrostreptomycin sulphate. After the