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Inability of dextran to release kinin in rats

Ankier & Starr (1967) showed the hypotensive response to intravenous dextran in rats to be probably mediated by histamine and 5-hydroxytryptamine. Lecomte & Damas (1968) now suggest that plasma kinins may have an accessory role in this anaphylactoid reaction. I now report that dextran does not release kinin in rats.

Male Wistar albino rats, 150–175 g (Wellcome Laboratories, Beckenham, and Agricultural Research Council, Compton) were tested for reactivity to dextran on three occasions (250 mg/kg, i.p., *M* 110,000), and those which showed peripheral oedema (reactors) were separated from non-reactors. Reactor rats were anaesthetized with pentobarbitone (40 mg/kg, i.p.) and injected with heparin (50 units/kg, i.v.). Blood pressure was recorded from the right common carotid artery with a Condon mercury manometer, and drugs injected into the right femoral vein.

Dextran (250 mg/kg) elicited a fall in blood pressure in reactor rats which lasted 40–60 min, after an initial delay in onset of 2–5 min. A similar response was produced by ellagic acid (5 mg/kg), an activator of Hageman factor and plasma pre-kallikrein (Margolis, 1958; Ratnoff & Crum, 1964), but with a quicker onset (1–2 min) and a shorter duration (10–15 min). Tachyphylaxis developed to repeated injections of ellagic acid, indicating a progressive consumption of the substrate for plasma kallikrein in the blood (substrate 1—Jacobsen, 1966). However, the administration of dextran to kininogen-depleted rats still caused a typical fall in blood pressure. Pretreating rats with Soya Bean Trypsin Inhibitor (SBT1, 100 mg/kg) reduced the hypotensive activity of ellagic acid by about 64%, whereas this concentration did not affect the action of dextran (Table 1). From these observations it seems unlikely that dextran activates plasma kinin-forming enzymes to a significant extent, since inhibition of plasma kallikrein with SBT1, or reducing the level of its substrate in the blood, did not modify the course of the reaction to dextran. On the other hand, both of these procedures attenuated the hypotensive action of ellagic acid, a compound which is known to activate plasma kallikrein. Another possibility also investigated was that dextran in some way liberated glandular

Table 1. *Effects on the blood pressure responses to dextran in reactor rats of soya bean trypsin inhibitor (SBT1, 100 mg/kg, i.v.) and ellagic acid, and of Trasylol (100 000 units/kg, i.v.) and pancreatic kallikrein*

Drug	dose (mg/kg)	Inhibitor	% fall in blood pressure (± s.e.) Untreated	After inhibition
Dextran	250	SBTI	58·8 ± 6·9	54·3 ± 2·3
Ellagic acid	5	SBTI	49·5 ± 4·8	17·8 ± 1·2*
Dextran	250	Trasylol	65·1 ± 9·2	58·2 ± 5·0
Pancreatic kallikrein	150	Trasylol	27·4 ± 2·4	13·4 ± 2·8*

* Inhibition = 64% ($P < 0.001$).
* Inhibition = 51% ($P < 0.005$).

kallikreins from tissue stores, which then released kinins from a separate plasma substrate (substrate 2—Jacobsen, 1966). Intravenous injections of pancreatic kallikrein (150 units/kg; Glumorin, Bayer) produced rapidly-developing and short-lasting reductions in blood pressure, but as many as eight consecutive doses usually had to be given to obtain a pronounced tachyphylaxis to this enzyme. Even when rats had been depleted of substrate 2—kininogen in this way, the degree of hypotension obtained with dextran in such animals lay within the normal range. In addition, rats previously treated with Trasylol (100,000 units/kg, i.v.; Bayer), an inhibitor of glandular kallikreins (Werle & Maier, 1952), showed a diminished reactivity to pancreatic kallikrein (51% inhibition) but not to dextran (Table 1). Thus, it is considered that glandular kallikreins do not play an active part in the blood pressure response to dextran in the rat.

Non-reactor rats have been found to be resistant to the blood pressure effects of injected dextran (Ankier & Starr, 1967), and yet in the present experiments they were found to be just as sensitive as reactors to intravenously-administered ellagic acid, pancreatic kallikrein and synthetic bradykinin (2·5–10 μg/kg; BRS 640, Sandoz). These results confirm earlier findings of the qualitative and quantitative similarities of the plasma kinin systems of the two kinds of rat (Ankier & Starr, 1967). In view of these similarities, it is difficult to account for reactivity on the basis of a selective liberation of plasma kinins, or non-reactivity as being a defect in the mechanism for kinin formation and release.

In conclusion, the above experiments show that neither the selective depletion of the substrates for kinin-forming enzymes in the blood, nor the selective inhibition of the enzymes themselves, modify significantly the vasodepressor property of dextran in the albino rat. The relative unimportance of plasma kinins in the early stages of the anaphylactoid syndrome is further emphasized by the apparent normality of the plasma kinin system in rats which failed to react to dextran. This is not to say that kinins may not be involved in the later process of oedema formation, when it is highly probable that a localized liberation of kinins, occurs secondary to the release of other chemical mediators, such as histamine and 5-hydroxytryptamine (Ankier & Starr, 1967; Greeff, 1968).

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