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On the action of bombesin on the kidney of the rat and the dog

Bombesin is the tetradecapeptide isolated from extracts of the skin of the European discoglossid frogs *Bombina bombina* and *Bombina variegata variegata* (Anastasi, Erspamer & Bucci, 1971).

We now report the action of bombesin on the kidney of the rat and the dog, and also on the renin-angiotensin system.

Bombesin produced a reduction of urine flow in the rat. In animals anaesthetized with ethanol (5 ml of 15% ethanol per 100 g weight) and then given an intravenous infusion of 2% ethanol (50 μl/min) the threshold dose of bombesin capable of reducing diuresis by intravenous infusion was 50 ng/kg per min; in conscious rats given a water load by oral route the threshold subcutaneous dose was 20–50 μg/kg.

Reduction in urine flow was accompanied by a reduction in glomerular filtration rats (creatinine clearance) and in renal plasma flow (*p*-aminohippurate clearance). In a typical experiment in which bombesin was infused for 30 min at a rate of 100 ng/kg per min reduction of urine flow was 80%, of glomerular filtration rate 75% and of renal plasma flow 68%. Fractional sodium reabsorption (C_{Na}/C_{Cr} %) decreased during antidiuresis, which was apparently counteracted by high sodium intake.

In conscious rats, both hydrated and non-hydrated, 100 μg/kg of bombesin given subcutaneously produced an increase of blood pressure (10–30 mm Hg) lasting more than 2 h. In rats anaesthetized with ethanol, the intravenous infusion of 100 ng/kg per min of bombesin for 30 min initially caused a rise in blood pressure (20–30 mm Hg) which was followed by slow decline and then, after the infusion was discontinued, by a return to normal levels or slight hypotension (10–20 mm Hg). Thus, changes of blood pressure could counteract, but not favour, bombesin antidiuresis.

The effect of bombesin on the dog kidney was intense. In animals anaesthetized with sodium pentobarbitone and given a 5% water load by stomach tube, the threshold dose of the polypeptide producing antidiuresis by rapid intravenous injection was about 0·1 μg/kg, by intravenous infusion 0·5 ng/kg per min, and by subcutaneous route 0·5 μg/kg. The effect was of rapid onset and its duration depended on the dose given. Tachyphylaxis readily occurred, with conspicuous differences from one animal to another. With low doses a fair dose response relation could sometimes be observed; with large doses tachyphylaxis was more prompt and intense. Generally, antidiuresis paralleled the rise in blood pressure produced by bombesin, especially in its duration.

As in the rat, antidiuresis was accompanied by reduction in glomerular filtration rate (creatinine clearance) and in renal blood or plasma flow (washout of ^{85}Kr and ^{3}H-*p*-aminohippurate clearance). The urine eliminated during moderate bombesin antidiuresis (20–50% reduction of urine flow) had a reduced concentration of sodium.

Results obtained in some typical experiments were as follows. 1 ng/kg per min of bombesin infused for 30 min elicited a 50% reduction of urine volume accompanied by a 50% reduction of creatinine clearance and a 48% reduction of *p*-aminohippurate clearance. Component I of the ^{85}Kr washout curve (outer cortical flow) was reduced

by 40–50%, while component II of the same curve (inner cortical flow plus outer medullary flow) showed a 15% increase (see Thorburn, Kopald & others, 1963).

3 ng/kg per min of bombesin infused for 30 min produced reductions of 90% in urine volume, of 93% in creatinine clearance and of 85% in *p*-aminohippurate clearance. Component I of the ^{85}Kr washout curve was reduced by 60–70%, whilst component II was increased by 20%.

At the above dose levels the effect of bombesin on the kidney was prompt and, after discontinuing the infusion, renal circulation and function returned to normal within 40–50 min.

Compared with bombesin, the antidiuretic effect of Val^5-hypertensin was at least 100 times less.

Bombesin given by intravenous route (rapid injection and infusion) nearly always produced a rise of blood pressure which, to some extent, was dose-dependent and was maintained as long as the infusion was continued. After the infusion was discontinued, return to basal levels was prompt for low doses, but took 20–50 min for large doses. Once again the antidiuretic effect of bombesin was counteracted rather than favoured by the effect of the polypeptide on the systemic blood pressure.

Reduction in outer cortical flow was accompanied by a conspicuous renin release, measured by *in vitro* production of angiotensin I, immediately followed by an increase in angiotensin II in arterial plasma. Both events were demonstrated by means of radioimmunological methods.

During the intravenous infusion of 3 ng/kg per min of bombesin for 30 min arterial plasma concentrations of renin activity increased up to 2 times, and of angiotensin II up to 2·5 times. The effect began after 5 min, and reached a peak after 20 min. Discontinuation of the infusion often produced a second peak of renin activity and angiotensin II concentration after 15 min, with return to basal levels within 60 min. Under the above conditions, the renin secretion, as inferred from the difference in renin activity concentration between femoral artery plasma and renal venous plasma multiplied by renal plasma flow, was 8 times the normal.

If bombesin was infused at rates above 8–10 ng/kg min^{-1} a complete blockade of glomerular filtration was observed, together with a limited increase of renin secretion. For example, in an experiment in which bombesin was infused over 4 h at 10 ng/kg per min, renin secretion increased at first slightly but then, beginning at the second hour, fell below the control values. Discontinuing the infusion, a conspicious increase of renin secretion was apparent after 15–30 min, fading away within 120–150 min.

Thus bombesin appears to act on the kidney mainly through a constriction of the afferent glomerular bed in the cortex. This, of course, does not exclude the possibility that the polypeptide has other sites of action.

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