# Anti-hypertensive and natriuretic effect of glucagon-like peptide 1 in Dahl S rats: a novel function for a pleotrophic hormone?

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The hormone glucagon-like peptide 1 (GLP-1) is produced as a proteolytic processing product of the preproglucagon molecule in the L cells of the small and large intestine, as well as in some areas of the brain. GLP-1 released from the gut is best known for its insulinotropic action. Following nutrient ingestion, in particular glucose and fatty acids it is released into the blood and stimulates β-cell insulin secretion in a glucose dependent manner. This effect is mediated after binding to a specific plasma membrane receptor of the G protein coupled receptor family [1]. The GLP-1 receptor (GLP-1R) is expressed not only in the pancreatic β-cell, but also in the brain, the lungs, the kidneys, the pituitary gland, the heart, the stomach and the small intestine. This widespread distribution of the GLP-1R suggested that GLP-1 may exert a large variety of biological actions. Indeed, we now know that GLP-1 administration inhibits gastric acid secretion and gastric emptying, induces satiety, decreases food intake, regulates surfactant secretion from type II pneumocytes, and increases thyroid-stimulating hormone and luteinizing hormone-releasing hormone release in a variety of animal and cellular models [2].

GLP-1 receptors are abundant in the kidney, but their role remains obscure. Recent studies by Roman *et al.* [3] shed some light on this issue, by demonstrating that GLP-1 increases natriuresis and diuresis in Sprague–Dawley rats due to inhibition of tubular sodium reabsorption.

In this issue of the journal, Yu *et al.* [4] extend their observations and describe a blood pressure-lowering effect of GLP-1 in a hypertensive rat model. Dahl salt-sensitive rats, when fed a high salt diet, develop hypertension. This increase in blood pressure is associated with sodium retention and volume expansion. Treatment of Dahl S rats with GLP-1 for 14 days almost completely abolished the salt-induced increase in blood pressure. Additional experiments indicated that GLP-1 had a diuretic and strong natriuretic action, resulting in a negative cumulative sodium balance [4].

Whether these effects of GLP-1 are mediated through renal GLP-1 receptors remains unanswered.

Could the extra-renal effects of GLP-1 have contributed to its anti-hypertensive action? In previous experiments, diuretic and natriuretic responses to GLP-1 were attenuated in denervated kidneys, suggesting that some effects of GLP-1 on the kidney may be centrally mediated [3]. Further experiments are required to address this issue.

In addition to its insulinotropic effect, GLP-1 has been suggested to improve insulin sensitivity [5,6]. Similar to other models of hypertension, Dahl S rats are insulin resistant, and improving insulin sensitivity may have beneficial effects on blood pressure. In the present study, glucose and insulin levels were not different in GLP-1 treated and control rats, but they represent unfortunately a poor index of insulin sensitivity. Euglycemic hyperinsulinemic clamp studies to assess the effects of GLP-1 on insulin sensitivity in Dahl-S rats would have provided interesting mechanistic data.

Finally, the authors show that GLP-1-treated Dahl S rats had reduced end-organ damage, in particular renal injury (with decreased microalbuminuria and proteinuria) and left ventricular hypertrophy, as well as improved

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endothelial function compared to control animals [4]. These effects are most likely related to the antihypertensive action of GLP-1 in this model, even though a direct effect of GLP-1 cannot be excluded.

The results contrast with previously published data showing that GLP-1 or GLP-1 receptor agonist administration acutely increased blood pressure and heart rate in rats [7,8] through a central neural action because it could be blocked by intracerebro-ventricular administration of GLP-1 receptor antagonists [9]. The origin of these discrepancies is not clear, but may be related to differences in the dose or duration (acute versus chronic) of GLP-1 administration, or differences in the animal models used (normal versus hypertensive animals). Additional experiments directly addressing these issues, particularly in humans, will help to resolve some of these questions. This is important because GLP-1 is under intensive investigation for its therapeutic use in type 2 diabetes mellitus. Indeed, GLP-1 is a very interesting candidate drug for this indication, because its insulinotropic actions are maintained in diabetic patients, and it has additional beneficial effects, such as decreasing food intake and promoting weight loss, inhibiting gastric emptying and glucagon secretion, and potentially increasing insulin sensitivity and β-cell proliferation [10]. Preliminary data on the metabolic effects of short-term administration of GLP-1 in diabetic patients are encouraging [11]. With the new data provided by Yu *et al.* [4], it is now important to carefully monitor arterial blood pressure in trials using GLP-1 for the treatment of patients with type 2 diabetes mellitus. To date, only limited data in a small number of subjects are available. Acute administration of GLP-1 increases blood pressure in healthy subjects [12], whereas blood pressure remained unchanged in diabetic patients treated over 6 weeks [11]. Clearly, long-term studies are needed to settle this issue and, ideally, such studies should include subjects with salt-sensitive forms of high blood pressure. Unfortunately, the therapeutic use of GLP-1 is limited by two important factors: its peptidic nature necessitates intravenous or subcutaneous administration and its half-life is extremely short due to rapid inactivation by dipeptidyl peptidase IV (DPP IV). New analogs with significantly longer half-lives [13,14] and inhibitors of DPP IV have been developed [15] that should help to overcome some of these limitations. With such new tools, it will be possible to test whether the antihypertensive actions of GLP-1 seen in Dahl salt-sensitive rats are also encountered in human disease states.

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