Biphalin, a non-addictive synthetic opioid, is hypotensive and improves renal perfusion in anaesthetised spontaneously hypertensive rat

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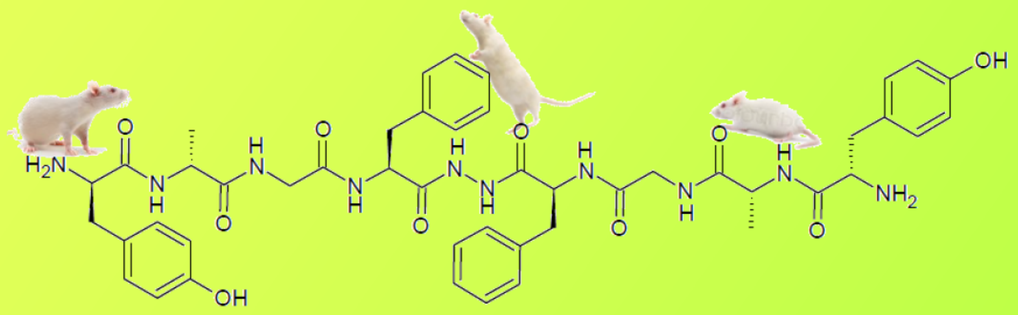
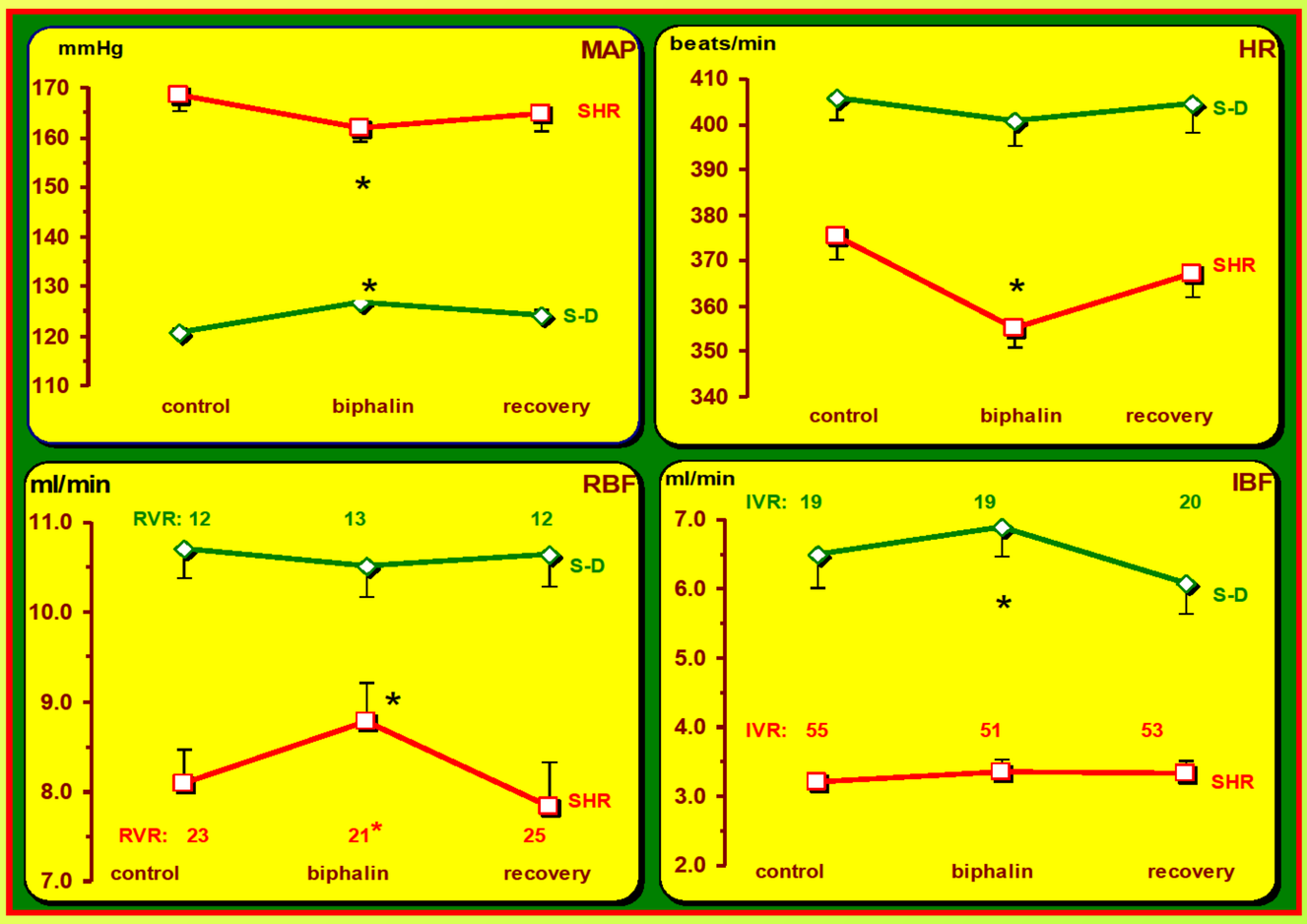
What is biphalin?

- a synthetic analogue (A.W. Lipkowski) related to enkephalin, an endogenous opioid
- a powerful analgesic, agonist of opioid receptors: μ, κ, δ
- non-addivtive (minimal physical dependence in animals)
- poor penetration of blood-brain barrier (vs morphine)



Background/Aim. Neurogenic factors contribute to the development of arterial hypertension, and opioids can inhibit nervous (mostly autonomous) signals to the cardiovascular system, and thereby lower arterial pressure (BP). Biphalin, a non-addictive synthetic opioid is of potential value in treatment of hypertension.

Our aim was **(1)** to examine effects of biphalin on BP in normotensive Sprague-Dawley (S-D) rats and in spontaneously hypertensive rats (SHR), and **(2)** to estimate the contribution of changes in cardiac output and peripheral vascular resistance to expected Bph-induced changes in BP. Particular attention was given to effect of Bph on perfusion of the kidney (RBF).



Material and Methods

Acute experiments with normotensive Sprague-Dawley (S-D, n = 15) and spontaneously hypertensive rats (SHR, n = 16)

#Anaesthesia: sodium thiopenthal, 100 mg/kg BW i.p.

Measurements:

mean aortic pressure (MAP) and heart rate (HR), via a femoral artery cannula, a pressure transducer and Stoelting manometer

renal blood flow (RBF), by a noncannulating flow probe (1 mm in diameter) placed on left renal artery, and Transonic TS420 flowmeter

iliac artery blood flow, to measure hind limb perfusion, by Transonic flowmeter and 1-mm probe placed on iliac artery

Vascular resistances in the kidney (RVR) and hind limb (IVR) were calculated as MAP**:** blood flow ($mmHg.ml^{-1}.min$)

Biphalin dosage: 150 μg/kg/h, infused i.v. during 20 min, bracketed by control and recovery measurement periods

Results

1. *Baseline values in SHR vs S-D rats*. Elevated MAP in SHR was associated with distinctly decreased HR values. Perfusion of the kidney (RBF) and hind limb (IBF) was lower in SHR than in S-D rats. Hypertension was associated with about 2fold greater renal (RVR) and 3fold greater hind limb (IVR) vascular resistance.

2. *Biphalin effects on systemic haemodynamics*. In SHR biphalin modestly but significantly decreased MAP and HR. In S-D rats MAP actually increased while HR did not change.

3. *Effects on renal perfusion*. Biphalin significantly increased RBF (+8.2%) but not IBF in SHR, no perfusion changes were observed in S-D rats. In SHR, RVR decreased slightly and in S-D it increased slightly (both changes significant). No major changes in IVR were seen in either rat group.

Conclusions

(1) In anaesthetized SHR, a hypertension model with pronounced neurogenic component, biphalin was modestly hypotensive.

(2) Since there were no major changes in the vascular resistance in the kidney or hind limb regions (RVR, IVR), the decrease in BP was probably caused by biphalin-induced decrease in the cardiac output.

(3) A substantial increase in RBF (despite a decrease in BP and renal perfusion pressure) indicates that in spontaneously hypertensive rats biphalin improves renal circulation.

The study was supported by the National Science Centre, Poland, project No. 2011/03/B/N24/02162