EFFECTS OF BUPHENIN ON THE RAT PORTAL VEIN

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Summary: The vasodilator and tocolytic substance buphenin (10 μmol/l) stimulated the spontaneous phasic activity of some (8 out of 18) isolated rat portal vein preparations; 0.1–1 mmol/l buphenin diminished or abolished the activity in all preparations. The isotonic and isometric contractions of portal vein in response to adrenaline, noradrenaline and phenylephrine (0.1–1 μmol/l) disappeared almost completely after addition of buphenin in equimolar concentrations, whereas acetylcholine contractions persisted. The beta-adrenergic blocking agents propranolol and dichloisoprenaline (10 μmol/l) only slightly antagonized the inhibitory effect of buphenin on the contractile responses to catecholamines. It is concluded that buphenin exerts dual action upon rat portal vein: the drug partially stimulates the beta-receptors and partially blocks the alpha-adrenergic receptors.

Key words: buphenin, mechanical activity, portal vein, mechanical activity, alpha- and beta-adrenergic receptors

INTRODUCTION

Buphenin (nylidrin), an arylalkylated catecholamine derivative, dilates peripheral arterial vessels and lowers the systolic and diastolic arterial blood pressure via beta-adrenergic stimulation (1,2,3,8,19). The drug also relaxes tracheal (1,2) and uterine-smooth muscle and it is used as a tocolytic substance (11,17). In addition buphenin produces alpha-adrenergic blockade of the seminal vesicle (12) and the vas deferens (1,2) and in guinea-pig and human detrusor muscle stimulates the spontaneous mechanical activity and contractions in response to electrical stimulation (13,14,15). In the present paper is described the effect of buphenin on the mechanical activity of isolated rat portal vein smooth muscle and its possible relation to alpha- and beta-adrenergic receptors is discussed.

The rat portal vein is constructed of longitudinal and circular smooth muscle layers (4) and shows spontaneous rhythmic activity due to myogenic automaticity (9). The inherent contractions are modified after stimulation of sympathetic (adrenergic) vasomotor fibers (10). The rat portal vein reacts to acetylcholine, adrenaline and noradrenaline
with augmented phasic activity and tonic contractions (3,5,6). The mechanical response of the portal smooth muscle to noradrenaline and to sympathetic nerve stimulation can be inhibited by treatment with phenoxybenzamine (alpha-adrenergic blockade) (3,10). The beta-receptor stimulating agent isoprenaline in low concentrations \((10^{-8}-10^{-7} \text{ g/ml (weight/volume)})\) reduces the individual (phasic) mechanical responses, while higher concentrations \((10^{-5} \text{ weight/volume})\) act like noradrenaline causing a temporary initial inhibition by followed contraction summation and fusion of the tension (3).

MATERIALS AND METHODS

Helical muscle strips (length: 10-20 mm) were cut from the portal vein of male albino rats (Wistar, pathogen-free, 300-350 g). The preparations were kept in an organ bath containing a modified Krebs-Henseleit solution (composition in mmol/l: NaCl 122; KCl 4.75; CaCl₂ 2.49; MgSO₄ 1.19; NaHCO₃ 15.48; KH₂PO₄ 1.49; glucose 11.5) at 37°C, aerated with a mixture of 95% O₂ and 5% CO₂. The mechanical activity of the portal vein was recorded under isotonic (preloaded with 100-200 mg, rotary motion transducer: Harvard Model 386, magnification 1:32) or isometric (force displacement transducer; Grass Model FTO 3C) conditions on a Schwarzer polygraph. The preparation was cautiously stretched until regular rhythmic activity appeared, giving a passive tension of 200-300 mg.

Drugs: acetylcholine chloride, adrenaline hydrogene tartrate, azapetine (Ilidar*, Hoffman-La Roche), buphenin (Dilatol*, Tropon), dichlorisoprenaline, propranolol hydrochloride, noradrenaline, phenylephrine.

RESULTS

After an adaptation time of about one hr the muscle tone of the portal vein preparation became stable for many hours. The size of the automous rhythmic contractions varied and the contractions often fused. The frequency of the visible spontaneous contractions was 2.86±0.33 (mean±S.E.M.) per min. Under isotonic conditions their amplitudes had a maximal value of 1.39±0.25% of the total length of the preparation (n=11), and under isometric conditions (n=13) a value of 85.76±19.07 mg tension per cm length of the preparations. After buphenin in concentrations of up to 1 μmol/l the portal muscle showed no visible changes in muscle tone or spontaneous activity (Figs. 1a and b). In some of the preparations 10 μmol/l also had no visible effect, while the contraction-amplitudes were augmented in 8 of 18 of the preparations. (Fig. 1b). Treatment with 0.1-1 μmol/l buphenin generally diminished or completely abolished the spontaneous

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activity (Fig. 1a). This inhibition was sometimes preceded by an increase in tone and contractile activity (Fig. 1c) (see Table I).

**Vena portae**

![Diagram](image)

**TABLE I:** Action of buphenin on the mechanical activity of rat portal vein (number of preparations in brackets).

<table>
<thead>
<tr>
<th>Reaction after buphenin</th>
<th>Muscle tone</th>
<th>Phasic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10^{-6} \text{ M}$</td>
<td>unchanged (7)</td>
<td>unchanged (7)</td>
</tr>
<tr>
<td>$10^{-5} \text{ M}$</td>
<td>unchanged (18)</td>
<td>(a) unchanged (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) augmented contraction-amplitudes (8)</td>
</tr>
<tr>
<td>$10^{-4} \text{ M}$</td>
<td>(a) unchanged (9)</td>
<td>(a) increased frequency and diminished contraction-amplitudes (5)</td>
</tr>
<tr>
<td></td>
<td>(b) elevated (6)</td>
<td>(b) abolition (10)</td>
</tr>
</tbody>
</table>
In most cases the muscle tone remained unchanged after buphenin (0.1 mmol/l), some preparations showed an elevated tone and/or a persistent phasic activity which was characterized by higher frequency and smaller contraction-amplitudes (Table I). The alpha-adrenolytic substance azapetine (10 μmol/l) and also the beta-adrenolytic substance propranolol (10 μmol/l) inhibited this increase in portal mechanical activity (Fig. 1c). In concentrations higher than 10 μmol/l these two adrenergic blocking substances had an effect similar to that of 0.1 μmol/l buphenin, i.e. they abolished the mechanical activity of the portal vein.

Adrenaline and acetylcholine in concentrations of 0.1-1 μmol/l caused reproducible tonic contractions and an increase in phasic activity of the portal muscle. Figure 2 shows

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**Figure 2:** Action of buphenin on the adrenaline and acetylcholine responses of rat portal vein under isometric and isotonic conditions (magnification 1:30): in contrast to the adrenaline contractions the acetylcholine contractions are not visible influenced by buphenin.
the action of buphenin on the isometric and isotonic test-contractions of the two hormones. Buphenin inhibited dose-dependently the adrenaline, noradrenaline and phenylephrine contractions and in equimolar concentrations almost completely abolished these reactions (30 preparations). In contrast to these findings the acetylcholine test-reaction to 0.1-1 μmol/l was not visibly changed by buphenin in equimolar concentrations (20 preparations). After 0.1 mmol/l buphenin the acetylcholine reaction to 1 μmol/l disappeared (5 preparations). Table II gives a quantitative analysis of the action of buphenin on the adrenaline and acetylcholine test-contractions.

**Fig. 3:** Antagonizing action of the β-adrenergic blocking agent propranolol on the buphenin inhibitory effect upon the adrenaline test-reaction.

The inhibitory effect of buphenin on the adrenaline and phenylephrine test-reaction (0.1-1 μmol/l) was only partially antagonized by propranolol or dichlorisoprenaline (1-10 μmol/l), (9 preparations, see Fig. 3). In preparations that had not been pretreated with buphenin, propranolol (0.1-10 μmol/l) had no visible influence on the adrenaline- and phenylephrine-test-contractions.
TABLE II: Inhibitory effect of buphenin on the contractile response of isolated rat portal vein to adrenaline and acetylcholine.

<table>
<thead>
<tr>
<th>Portion vein</th>
<th>Contracting agent</th>
<th>n =</th>
<th>Mean length of preparations (mm)</th>
<th>Mean tension (mg) or shortening (%)</th>
<th>Inhibitory action of buphenin on the contraction in % (reaction after contracting agent = 100 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>45.20±13.96</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td>Adrenaline 10⁻⁶ M</td>
<td>8</td>
<td>12.7±1.2</td>
<td>80.13±85.69</td>
<td>86.40±4.91</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Acetylcholine 10⁻⁶ M</td>
<td>6</td>
<td>12.8±2.1</td>
<td>16.11±4.28</td>
<td>16.11±4.28</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td>&gt;0.05</td>
<td>25.00±14.43</td>
<td>&gt;0.01</td>
</tr>
<tr>
<td></td>
<td>Adrenaline 10⁻⁶ M</td>
<td>8</td>
<td>13.0±1.6</td>
<td>4.41±1.22</td>
<td>91.42±3.28</td>
</tr>
</tbody>
</table>

DISCUSSION

Perfusion of isolated dog liver with buphenin decreases both the portal venous flow and the ratio of portal vein outflow to total hepatic outflow, while the hepatic arterial flow is increased. Propranolol abolishes the effect of buphenin on the hepatic arterial flow (beta-adrenergic blockade) and further diminishes the portal venous flow (30). These findings are in accordance with our observation that buphenin augments the spontaneous mechanical activity in the rat portal vein and that propranolol in low concentration does not antagonize this effect. It seems that buphenin, azapetine and propranolol in high concentrations (100 μmol/l) act unspecifically on the portal mechanical activity because all these drugs inhibit the phasic contractions. The nature of the stimulatory and inhibitory effects of buphenin on the portal spontaneous (phasic) activity is not clear.

Buphenin strongly inhibits the catecholamines-test-contractions whereas the contractions in response to acetylcholine and to potassium and 5-hydroxytryptamine are only diminished (16). These findings can be explained by the alpha-adrenergic blocking properties of buphenin (1,2,12). On the other hand it is evident that buphenin also possesses some beta-adrenergic stimulatory action on the portal vein since propranolol and dichlorisoprenaline partially antagonized the inhibitory action of buphenin on the contractile response to adrenaline. This beta-adrenergic effect of buphenin in the rat portal vein is slight compared to that of isoprenaline: this drug produces a relaxation in canine veins from various organs preconstricted with noradrenaline, 5-hydroxytryptamine and histamine (18) and...
also in untreated rat portal vein (3) and in rabbit aortic strip (7) via stimulation of beta-adrenergic receptors of the venous smooth muscle.

REFERENCES