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Signal propagation via gap junctions, a key step in the regulation of liver metabolism by the sympathetic hepatic nerves

Florian G. Seseke, Andreas Gardemann and Kurt Jungermann

Institut für Biochemie, Universität Göttingen, Humboldtallee 23, D-3400 Göttingen, Germany

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Cell-to-cell communication via gap junctions has been proposed to be involved in the metabolic actions of sympathetic liver nerves in the rat. The effects of hepatic nerve stimulation and noradrenaline-, $PGF_{2\alpha}$- and glucagon infusion on glucose metabolism and perfusion flow were studied in perfused rat liver in the absence and presence of the gap junctional inhibitors, heptanol, carbenoxolone and (4β)phorbol 12-myristate 13-acetate (4βPMA). (i) Stimulation of the hepatic nerve plexus increased glucose output, decreased flow and caused an overflow of noradrenaline into the hepatic vein. (ii) Heptanol completely inhibited not only the nerve stimulation-dependent metabolic and hemodynamic alterations but also the noradrenaline overflow. Thus the heptanol-dependent inhibitions were caused primarily by a strong impairment of transmitter release. (iii) Carbenoxolone inhibited the effects of neurostimulation on glucose metabolism partially by about 50%, whereas it left perfusion flow and noradrenaline overflow essentially unaltered. (iv) 4βPMA reduced the nerve stimulation-dependent enhancement of glucose release by about 80% but the noradrenaline-dependent increase in glucose output only by about 30%; the increase in glucose release by $PGF_{2\alpha}$ and by glucagon remained essentially unaltered. 4βPMA reduced the nerve stimulation-dependent decrease in portal flow by about 35% but did not affect the noradrenaline- and $PGF_{2\alpha}$-elicited alterations, nor did it alter noradrenaline overflow. The results allow the conclusion that gap junctional communication plays a major role in the regulation of hepatic carbohydrate metabolism by sympathetic liver nerves, but not by circulating noradrenaline, $PGF_{2\alpha}$ or glucagon.

Hepatic nerve; Inhibitor of gap junction; Hepatic glucose metabolism; Hepatic hemodynamics; Liver perfusion

1. INTRODUCTION

The liver is innervated by sympathetic and parasympathetic nerves, containing efferent and afferent fibres. The vegetative nerves reach the liver via the anterior plexus around the hepatic artery and the posterior plexus around the portal vein [1–5]. Noradrenaline and adrenaline, released from peripheral synapses via overflow and from the adrenals, respectively, also reach the organ with the circulating blood; they could act via α_1-, α_2- and β_2-receptors [6,7].

In perfused rat liver, stimulation of the nerve plexus around the portal vein and the hepatic artery caused an increase in glucose and lactate output [6–10] and urate and allantoin formation [11], a decrease in ketogenesis [12], urea release and ammonia uptake [13] as well as oxygen utilization [14,15]. Furthermore, nerve stimulation decreased [6–10] and redistributed [15] flow intrahepaticly and caused an overflow of noradrenaline into the hepatic vein [6,7,16]. All nerve actions required extracellular calcium [8,17]. Noradrenaline released by nerve stimulation from the nerve endings [16] acted via sympathetic α_1-receptors [6,7]. Since inhibitors of prostanoid synthesis inhibited the nerve actions [18] and since prostaglandins mimicked these actions [19], it was proposed that prostaglandins like $PGF_{2\alpha}$ released from non-parenchymal cells served as 'inter-transmitters' in the nervous signal chain [19]. Noradrenaline and prostanoids caused the alteration in metabolism and hemodynamics via their specific receptors [20–23].

It was found that the content of noradrenaline in liver tissue and the amounts released upon nerve stimulation were much higher in livers of guinea pig and tree shrew than in rat [24]. These findings were in line with anatomical observations that in guinea pig and tree shrew nearly all liver cells possess nerve contacts while in the rat only a few periportal cells are innervated [25,26]. Since the carbohydrate metabolism in guinea pig and tree shrew liver was regulated by nerve stimulation similarly to rat liver [24], a mechanism had to be postulated which would compensate the rare hepatic innervation in rat liver and thereby cause the same effective activation of glycogenolysis as in guinea pig and tree shrew liver. Thus, it was proposed that the nerve signal is propagated through gap junctions via electrotonic coupling [8,9,24–26].

It was the object of the present investigation to study the role of gap junctions in the nervous signal chain in the perfused rat liver by using gap junctional inhibitors. Various substances such as heptanol [27–30], glycyrrhetinic acid derivatives like carbenoxolone [31,32] and (4β)phorbol 12-myristate 13-acetate (4βPMA) [29, 30,33,34] have been reported to cause closure of gap

Correspondence address: F.G. Seseke, Institut für Biochemie, Universität Göttingen, Humboldtallee 23, D-3400 Göttingen, Germany.

junctions in a variety of cell systems [27–34]. It was found that heptanol completely inhibited the metabolic and hemodynamic nerve actions but also the noradrenaline overflow, while carbenoxolone and PMA impaired the metabolic nerve effects without modifying noradrenaline overflow. The present results allow the conclusion that gap junctions are involved in the signal chain of sympathetic metabolic nerve action in rat liver. While this work was in progress, a study appeared which came to the same conclusion using a quite different approach [35].

2. MATERIALS AND METHODS

2.1. *Materials*

All chemicals were of reagent grade and from commercial sources. Enzymes, coenzymes, substrates and bovine serum albumin were purchased from Boehringer (Mannheim, Germany), except glucose dehydrogenase, which was from Merck (Darmstadt, Germany). l-Noradrenaline bitartrate and glucagon were from Serva (Heidelberg, Germany). 1-Heptanol, prostaglandin $F_{2\alpha}$, carbenoxolone and (4β)phorbol 12-myristate 13-acetate (4βPMA) were purchased from Sigma (Deisenhofen, Germany).

2.2. *Animals*

Male Wistar rats (220–300 g) were obtained from Winkelmann (Borchen, Germany). At least 1 week before the experiments, they were subjected to a 12 h day–night rhythm with free access to water and food (standard rat diet of Ssniff, Soest, Germany). All experiments were started between 09.00 and 10.00 h. The animals were anaesthetized by intra-peritoneal injection of pentobarbital (100–150 mg/kg body weight).

2.3. *Liver perfusion*

The liver was perfused in situ without recirculation via the portal vein in a 37°C cabinet using an erythrocyte-free Krebs–Henseleit bicarbonate buffer containing 5 mM glucose, 2 mM lactate, 0.2 mM pyruvate and 0.5% bovine serum albumin. The medium was equilibrated with a gas mixture of 95% (v/v) O_2 and 5% (v/v) CO_2. Perfusion pressure was constant at about 15 cm H_2O with a flow rate of 3.8–4.5 $ml \cdot min^{-1} \cdot g\ liver^{-1}$ under basal conditions. Perfusion flow was measured by fractionating the effluent at intervals of 0.5 min. All experiments were started after a 30 min pre-perfusion.

2.4. *Nerve stimulation and infusion of signal compounds*

The hepatic nerves were stimulated (12 V, 10 Hz, 0.5 ms) with a bipolar platinum wire electrode placed around both the portal vein and the hepatic artery. The latter vessel was not perfused but still joined to the portal vein. Noradrenaline, $PGF_{2\alpha}$ and glucagon (final concentration 1 μM, 5 μM and 1 nM, respectively) were dissolved in physiological saline and then diluted to an appropriate concentration for infusion in Krebs–Henseleit bicarbonate buffer containing 0.1% bovine serum albumin. The concentration of the stock solutions which were used for infusion was about 60-fold higher than the final concentration in the portal vein.

2.5. *Gap junctional inhibitors*

Heptanol (final concentration 2 mM) and carbenoxolone (final concentration 50 μM) were added directly to the perfusion medium. 4βPMA (final concentration 10 nM) was dissolved in dimethylsulfoxide (DMSO) and then diluted to an appropriate concentration for infusion in Krebs–Henseleit bicarbonate buffer containing 0.1% bovine serum albumin.

2.6. *Determination of metabolites and noradrenaline*

Metabolites were measured with standard enzymatic techniques: glucose with glucose dehydrogenase (Merck glucose system) [36]. Noradrenaline was quantitated electrochemically after separation by HPLC using the Waters system [37].

2.7. *Evaluation*

The metabolic effects were evaluated by calculating the area under the curve (AUC) of the alterations in glucose balance and perfusion flow. When baselines of glucose balance after infusion differed from those of the pre-stimulation period, both baselines were connected for evaluation of the area under the curve as indicated in Fig. 1. Significance was tested with Student's t-test for paired or unpaired values as indicated.

3. RESULTS

3.1. *Effects of nerve stimulation, noradrenaline, $PGF_{2\alpha}$ and glucagon on hepatic metabolism and hemodynamics*

Rat livers were perfused in situ with an erythrocyte-free Krebs–Henseleit bicarbonate buffer for 65 min. Hepatic nerves were stimulated (12 V, 10 Hz, 0.5 ms) (Fig. 1A) and noradrenaline (1 μM), $PGF_{2\alpha}$ (5 μM) and glucagon (1 nM) were infused for periods of 2 min (not shown). Electrical stimulation of the hepatic nerves increased glucose output, caused an overflow of noradrenaline into the hepatic vein and reduced portal flow (Fig. 1A). Similar alterations in glucose balance and in flow were caused by noradrenaline and $PGF_{2\alpha}$. Glucagon also increased glucose output, but had no effect on hepatic flow (not shown).

3.2. *Effects of nerve stimulation on hepatic metabolism and hemodynamics in the presence of gap junctional inhibitors*

So far, several substances such as heptanol, octanol, the anesthetics halothane and ephrane [29], glycyrrhetinic acid and its hydrophilic derivative carbenoxolone [31,32], phorbol esters such as (4β)phorbol 12-myristate 13-acetate (4βPMA) [29,30,33,34] and CO_2 [29,38] have been found to induce closure of gap junctions in a variety of cell systems. Since an adequate oxygen supply is a prerequisite for the metabolic and hemodynamic effects of sympathetic nerve stimulation [39], it was impossible to use CO_2 as gap junctional inhibitor in perfused liver. Thus, heptanol, carbenoxolone and 4βPMA were selected.

3.2.1. Heptanol. Heptanol (2 mM) added from the 1st to the 20th min of perfusion steadily enhanced basal glucose output (Fig. 1D) without influencing hepatic flow. Heptanol completely inhibited the nerve stimulation-dependent metabolic and hemodynamic alterations (Fig. 1D, Table I) but it did not modify the changes by noradrenaline and glucagon (not shown). Apparently, the inhibitory effects of heptanol were not caused primarily by interactions with hepatocellular gap junctions but by effects on synaptic functions, since in the presence of heptanol the overflow of noradrenaline was nearly completely suppressed (Fig. 1D, Table I).

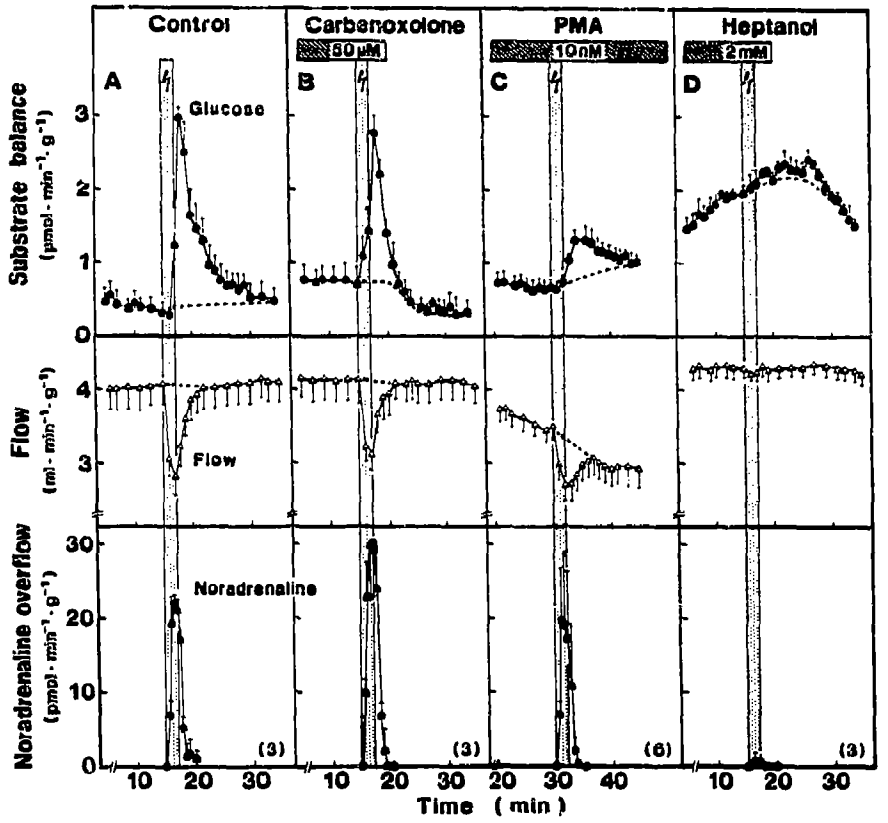

Fig. 1. Effects of neurostimulation on hepatic glucose metabolism, portal flow and noradrenaline overflow in the absence and presence of gap junction inhibitors. Livers were perfused via the portal vein without re-circulation with Krebs–Henseleit bicarbonate buffer containing 5 mM glucose, 2 mM lactate and 0.2 mM pyruvate. Carbenoxolone, heptanol or 4βPMA were added to the final concentrations and for the times indicated. The hepatic nerves were stimulated (12 V, 10 Hz, 0.5 ms) for 2 min each as shown. Substrate balance is given by [concentration in portal vein − concentration in hepatic vein (μmol·ml^{-1})] × flow (ml·min^{-1}·g^{-1}). Values are means ± S.E.M. of the number of experiments given in parentheses.

All inhibitory effects of heptanol on hepatic nerve stimulation were found to be reversible. 30 min after the first nerve stimulation and 25 min after the cessation of heptanol application a second stimulation resulted in similar effects on glucose balance, perfusion flow and noradrenaline overflow as in the controls (not shown).

Table I

Alteration in glucose balance, portal flow and noradrenaline overflow by hepatic nerve stimulation in the absence and presence of the gap junctional inhibitors, carboxolone, 4βPMA and heptanol

Parameters	Alterations			
	Control (3/3)	Carbenoxolone (3/3)	4βPMA (6/4)	Heptanol (3/3)
Glucose				
μmol·g^{-1}	10.70 ± 1.32	5.87 ± 0.48**	2.27 ± 1.01**	0.91 ± 0.19**
%	–	55	21	9
Flow				
ml·g^{-1}	−4.12 ± 0.64	−2.96 ± 1.28	−2.54 ± 1.01*	−0.03 ± 0.02**
%	–	72	62	1
Noradrenaline overflow				
pmol·g^{-1}	61 ± 10	79 ± 20	52 ± 25	1.63 ± 1.36**
%	–	130	85	3

Data represent the areas under the curves taken from Fig. 1 and are means ± S.E.M. of the number of experiments given in parentheses (glucose, flow/noradrenaline overflow). Statistics: Student's t-test for unpaired values; significant differences to the control values are indicated by *$P < 0.05$, **$P < 0.01$.

3.2.2. Carbenoxolone. Carbenoxolone (50 μM) added from the 1st to the 20th min of perfusion inhibited the stimulation-dependent increase in glucose output by about 50% (Fig. 1B, Table I). Higher concentrations of the glycyrrhetinic acid derivative (100 μM) did not cause a stronger inhibition (not shown). Carbenoxolone did not alter the nerve stimulation-dependent noradrenaline overflow and decrease in perfusion flow (Fig. 1B, Table I).

The inhibitory effect of carbenoxolone was almost completely reversible, since a second nerve stimulation 30 min after the first stimulation and 25 min after cessation of carbenoxolone infusion caused an only slightly and insignificantly weaker increase in glucose output than in the controls (not shown).

3.2.3. (4β)Phorbol 12-myristate 13-acetate (4βPMA). 4βPMA (10 nM) infused from the 11th min of perfusion until the end of the experiment slightly enhanced basal glucose balance and moderately decreased perfusion flow (Fig. 1C; broken lines). Therefore, in the presence of 4βPMA glucose output and portal flow altered by nerve stimulation (Fig. 1C), noradrenaline, $PGF_{2\alpha}$ and glucagon (not shown) did not reach basal pre-stimulation values again. 4βPMA inhibited the nerve stimulation-dependent increase in glucose release by about 80% (Figs. 1C and 2; Table I) but did not affect noradrenaline overflow into the hepatic vein (Fig. 1C, Table I). 4βPMA reduced the noradrenaline-dependent enhancement of glucose output by only 30% (Fig. 2), and had no influence on the increase in glucose release by $PGF_{2\alpha}$ (Fig. 2) or by glucagon (not shown). 4βPMA reduced the nerve stimulation-dependent decrease in portal flow by about 35% (Figs. 1C and 2; Table I), but did not alter the flow reductions caused by noradrenaline and $PGF_{2\alpha}$ (Fig. 2).

In an additional series of experiments it was shown that the inhibitory effects of 4βPMA on glucose balance and perfusion flow were not reversible. A second neurostimulation 30 min after the first stimulation and 25 min after cessation of 4βPMA did not cause any increase in glucose output and reduction of perfusion flow (not shown).

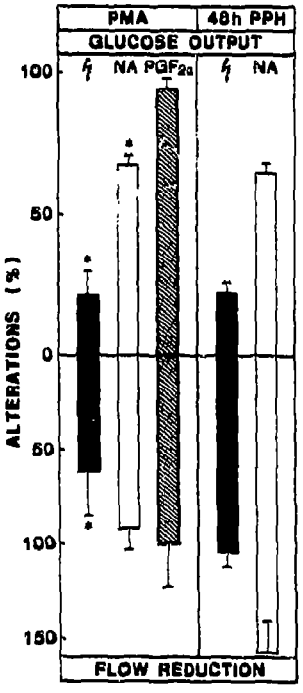

Fig. 2. Noradrenaline- and nerve stimulation-dependent alterations in hepatic glucose output and portal flow reduction in the presence of 4βPMA and in regenerating liver tissue. Normal rat livers were perfused and the substrate balance was determined as described in Fig. 1A and 1C. Hepatic nerves were stimulated and noradrenaline (NA, 1 μM) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 5 μM) were infused from the 31st to the 32nd min of perfusion with or without addition of 4βPMA at the 11th min. For easier comparison data from a previous study are shown: regenerating rat livers were perfused 48 h after partial hepatectomy (48 h PPH) [35]. Hepatic nerves were stimulated (20 V, 10 Hz, 2 ms) and noradrenaline (1 μM) was infused from the 31st to the 40th min of perfusion [35]. Alterations in the absence of 4βPMA were set equal to 100%. Values are means (areas under the curves) ± S.E.M. of 3 experiments (4βPMA) or 4 experiments (PPH) [35]. Statistics: Student's *t*-test for unpaired values: $^{*}P < 0.05$.

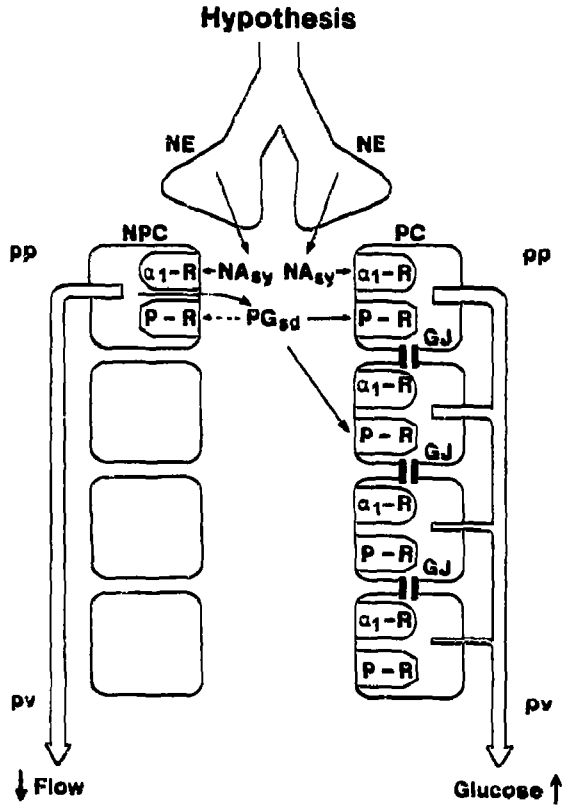

Fig. 3. Hypothetical scheme of the signal chain from nerve stimulation to alteration in metabolism and hemodynamics in rat liver: signal propagation via gap junctions from the periportal to the perivenous area. GJ, gap junctions; NE, nerve ending; NPC, non-parenchymal cell; PC, parenchymal cell; NA_{sy}, synaptic noradrenaline; PG_{sd}, prostaglandins in the space of Disse; P-R, prostaglandin receptor; α_1-R, α_1-receptor.

4. DISCUSSION

It was shown in the present study with the perfused rat liver that three different gap junction inhibitors impaired the nerve stimulation-dependent increase in glucose output: heptanol prevented the metabolic change completely, carbenoxolone lowered it by 50% and 4βPMA by 80% (Fig. 1, Table I).

4.1. *Specificity of the inhibitory effects of heptanol, carbenoxolone and 4βPMA*

Heptanol is a well-established reversible inhibitor of cell-to-cell communication via gap junctions. It could act either directly on the junctional proteins, the connexins, or indirectly via an increase in intracellular Ca^{2+} or H^+ or via a perturbation of membrane fluidity [27,28]. The latter mechanism seems more likely. In the present study 2 mM heptanol totally blocked the metabolic and hemodynamic nerve actions (Fig. 1, Table I). It probably inhibited the gap junctional functions, yet it also inhibited nerve terminal activity: noradrenaline overflow, which is the result of release and re-uptake, was reduced essentially to zero (Fig. 1; Table I), most likely by preventing release rather than by increasing re-uptake. Thus, heptanol in the complex system of an intact organ was not the specific gap junction inhibitor that is generally believed to be. The results of the heptanol experiments do not allow any conclusion on a possible role of gap junctions in the metabolic actions of the sympathetic hepatic nerves.

Glycyrrhetinic acid derivatives represent a novel class of inhibitors of gap junctional communication [31,32]. They bind to mineralcorticoid and glucocorticoid receptors; it is unlikely, however, that this binding plays a role in the inhibition of gap junctions. Rather, it has been proposed that they intercalate into the plasma membrane and bind to the gap junction connexins inducing a conformational change which results in closure of the channels [32]. In the present investigation 50 μM carbenoxolone inhibited the metabolic nerve actions by 50% (Fig. 1, Table I) without affecting noradrenaline overflow. Higher 100 μM concentrations did not cause a stronger inhibition. Thus, it would appear that signal propagation through gap junctions was involved in 50% of the nerve stimulation-dependent metabolic alterations.

Diacylglycerol and phorbol esters such as 4βPMA appear to cause a protein kinase C-mediated decrease in gap junctional permeability, while cAMP seems to elicit a protein kinase A-dependent increase [33,34,40,41]. Moreover, 4βPMA has been found to inhibit α_1-receptor-dependent signal chains via a protein kinase C-mediated desensitization of the receptor or the respective G-protein [42,43]. In this study 10 nM 4βPMA reduced the metabolic actions of nerve stimulation by 80% without affecting noradrenaline overflow. Yet it lowered the effects of the α_1-agonist noradrenaline only by 30% and left those of prostaglandin $F_{2\alpha}$ unaltered (Fig. 2). A plausible explanation of these findings is that 4βPMA inhibited 30% of the metabolic nerve effects by de-sensitizing the α_1-receptors and another 50% by closing the gap junctions. Thus, again gap junctional communication would appear to be involved in 50% of the metabolic nerve actions.

4.2. *Comparison of the nerve effects in normal, carbenoxolone or 4βPMA treated liver and in regenerating liver*

During the present work a study on the possible involvement of gap junctions in the action of sympathetic liver nerves was published using a quite different approach [35]. The content of connexin 32, a major component of gap junctions in rat liver, was found to be decreased to 25% of the control level in regenerating liver 48 h after a two-thirds partial hepatectomy. The nerve stimulation-dependent increase in glucose output was lowered by 80%, while the decrease in hepatic flow and noradrenaline overflow remained unaltered. Yet the noradrenaline-elicited enhancement of glucose release was reduced only by 30% and the decrease in flow was even more pronounced (Fig. 2). These results are identical to those obtained in the present study with normal but 4βPMA-treated rat livers (Fig. 2); they are similar to those obtained with normal, carbenoxolone-treated livers. The results with the regenerating liver also led to the conclusion that in rat, liver gap junctions assist signal propagation through intercellular communication following sympathetic nerve stimulation.

4.3. *Hypothesis for the mechanism of action of sympathetic liver nerves in the rat*

The model is based on the following observations: in rat liver, sympathetic nerves appear to innervate only a few parenchymal and non-parenchymal cells in the proximal periportal zone [25,26]. Rat liver is very rich in gap junctions [25,26]. Metabolic and hemodynamic effects of the sympathetic liver nerves are mediated via α_1-receptors [4,6,7], inhibited by inhibitors of prostanoid synthesis [18] and mimicked by prostaglandins but not thromboxanes [19]. Noradrenaline as well as prostaglandin $F_{2\alpha}$ stimulate glucose release from isolated parenchymal cells via an increase in inositol 1,4,5-trisphosphate and thence in glycogen phosphorylase a [44].

Noradrenaline released from the nerve terminals binds to α_1-receptors on the parenchymal and the non-parenchymal cells. In the proximal parenchymal cells noradrenaline increases glucose release and triggers a signal, which is propagated through the gap junctions to the more distal parenchymal cells to increase glucose output there. In the proximal non-parenchymal cells (sphincters) noradrenaline elicits contraction and thus reduces sinusoidal flow; in addition it causes the release of prostaglandins into the space of Disse. The prosta-

glandins in turn bind to the prostaglandin receptors on both the parenchymal and non-parenchymal cells. Since prostaglandins released from non-parenchymal cells are degraded very rapidly in liver [44] they do not reach distal cells. In the proximal parenchymal cells, prostaglandins further increase glucose release and probably also trigger a signal, which is propagated through gap junctions. In the proximal non-parenchymal cells prostaglandins 'autocatalytically' re-inforce contraction and thus reduction of sinusoidal flow. Thus the sympathetic nerves increase glucose release mainly in the periportal half of the parenchyma in line with the concept of metabolic zonation [45].

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