Korean J. of Pharmacology
Vol. 24, No. 1, pp.63-70, 1988

Altered Functions of Adrenoceptors in Splanchnic Vascular Beds in Portal Hypertensive Rat Model: Effect of Propranolol

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ABSTRACT

Alterations in splanchnic circulatory hemodynamics along with reactivities to the alpha adrenoceptor agonists were assessed in association with the preventive effects of propranolol 10 days after portal ligation. Decreases in precapillary resistance (Ra) and postcapillary resistance (Rv) along with increases in mesenteric blood flow (MBF) and capillary pressure (CP) were observed in conjunction with an increment of splenic pulp pressure (SPP). Dose-dependent increase in Rv in response to noradrenaline, increases in Ra and RV to adrenaline, and increases in superior mesenteric arterial pressure (SMAP), Ra and Rv to phenylephrine observed in sham group were significantly attenuated by portal vein stenosis. In PPL-3 group (propranolol 3 mg/kg, i.p. three times daily for 10 days), MBF was significantly decreased in association with decrease in mesenteric venous pressure (MVP) when compared with those of protal ligated (PL) group, and decreased Ra and Rv in PL group were recovered toward the values of sham group. Likewise, in PPL-1 group (propranolol 5 mg/kg, i.p. once daily for 10 days), the pressor response of Rv to adrenaline was recovered up to the level of sham group. Thus, it is suggested that decreases in Ra and Rv in association with increases in MBF and CP may have a close relevance to the increased SPP, and the changes in circulatory hemodynamics and vascular reactivities were effectively reversed by longterm propranolol treatment. Based on these results, it is concluded that these changes observed in portal hypertension are closely related with the altered functions of the adrenoceptors in the splanchnic vascular beds.

Key Words: Portal hypertension, Adrenoceptors, Splanchnic circulation

INTRODUCTION

As typical changes in splanchnic ciruclatory hemodynamics in the portal hypertensive rat models, an increase in blood flow to splanchnic organs and a decrease in splanchnic and systemic vascular resistances are characteristically associated with an elevation of portal venous pressure (Murray *et al.*, 1958; Blanchet and Lebrec, 1982; Groszmann and Atterbury, 1982; Witte and Witte, 1983; Vorobioff *et al.*, 1983; 1984). Generally, in portal hypertension, the preexisting collataral veins dilate and form portal-systemic shunts, thereby carrying the major portions of blood flow away from portal into systemic veins. These naturally occurring shunts counteract the increased resistance to portal blood flow. Nevertheless, the portal hypertension remains to persist (Rousselot *et al.*, 1959; Wexler and MacLean, 1975). In this regard, two speculations have been advanced to explain these hemodynamic characteristics. One is the backward flow theory: this hypothesis attributes portal hypertension solely to increased portal venous resistance, therefore implicating a passive congestion within portal venous system (Bradley *et al.*, 1952; Moreno *et al.*, 1967). The other is the forward flow theory: it is ascribed to an increased splanchnic blood flow that maintains the portal

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hypertension (Gitlin *et al.*, 1970; Witte *et al.*, 1974). These hemodynamic alterations in chronic portal hypertension have been reported not only in the animal experiments with carbon tetrachloride -induced cirrhosis (Chojkier and Groszmann, 1981; Kitano *et al.*, 1982) or biliary cirrhosis (Bosch *et al.*, 1983), but also in the pathologic conditions associated with portal hypertension in humans (Murray *et al.*, 1958; Epstein *et al.*, 1977).

In portal hypertension, propranolol has been chronically tried for reducing the portal venous flow on the baisis of beta 1-and beta 2-adrenoceptor blocking action (Kroeger and Groszmann, 1985). Lebreç *et al.* (1981) and Sϕgaard (1981) have reported that longterm propranolol treatment markedly reduced recurrent gastrointestinal bleeding in patients with cirrhosis. In contrast with these results, Burroughs *et al.* (1983) have advocated its use to be limited in clinical trials. Furthermore, the mechanisms underlying many of these changes in the splanchnic hemodynamics in portal hypertensive rats are not well identified.

In the present study, it was designed to investigate the splanchnic hemodynamic changes occurring and the alterations in the reactivities to vasoactive agents 10 days after portal ligation in rats, and further, effect of propranolol treatment on these changes was evaluated.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 350-400 g were fasted for 18-24 hours.

Portal ligation

Rats were anesthetized with secobarbital sodium (30 mg/kg, i.p.). After an incision of midline of abdomen, the common portal vein was dissected free of surrounding tissues and a ligature of 2-0 silk was placed around the vein. A 23-gauge blunt end needle was placed alongside the vein, and the ligature was tied snugly to the needle and vein. The needle was subsequently removed to yield stenosis of the portal vein. The abdominal incision was closed with suture. Rats were allowed to recover from anesthesia and returned to the vivarium. Ten days later, the animals were used for experiments. Sham-operated animals, whose portal vein was isolated but not stenosed, served as controls.

Experimental groups

The animals were divided into the following four experimental groups

1. Sham-operated rats (Sham)
2. Portal-ligated rats (PL)
3. Portal-ligated rats with propranolol treatment
   - 3.1. PPL-1: Propranolol was administered with a dose of 5 mg/kg i.p., once daily for 10 days.
   - 3.2. PPL-3: Propranolol with a dose of 3 mg/kg i.p., three times daily for 10 days

Determination of splanchnic hemodynamics

Rats were anesthetized with ethyl carbamate (urethane, 1.0 g/kg, i.p.). A tracheostomy was performed to ensure a patent airway. The abdomen

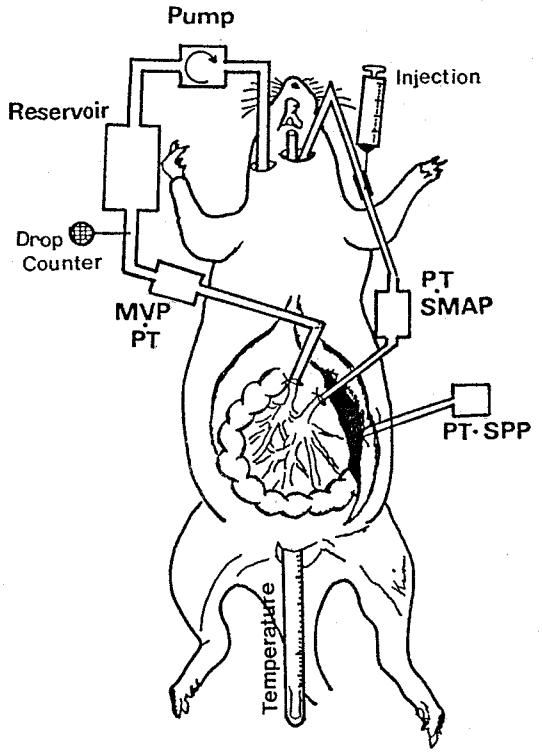

Fig. 1. Diagram of preparations for studying intestinal circulation. Autoperfusion from carotid artery to superior mesenteric artery and pump perfusion from mesenteric vein to jugular vein were installed. PT : pressure transducer.

was opened along the midline and the abdominal contents were covered with warm saline-soaked gauge and plastic wrap to prevent dryness. An intravenous injection of heparin (200 I.U./100 g) was made immediately before cannulation of the vessels. An arterial circuit was established between carotid and superior mesenteric arteries (Fig. 1). A T-tube was interposed within the arterial circuit, which allowed continuous monitoring of SMAP and measuring the reactivity of mesenteric vascular bed to various vasoactive agents. After a period of reperfusion, the artery was occluded and a large polyethylene cannula was rapidly inserted into the superior mesenteric vein. The venous outflow was drained into a reservoir before being returned to the systemic ciruclation though the internal jugular vein by peristaltic pump. MBF was estimated by drop counter and MVP was monitored via a T-tube connected to a pressure transducer (Statham, P23ID). SPP was firstly measured and in PL group, the rats with SPP less than 10 mmHg were discarded. In each experiment, the another whole blood was previously collected from the same group rats and used to compensate for the blood loss.

CP was determined using the venous occlusion technique (Granger *et al.*, 1983). Upon a sudden and brief occlusion of the superior mesenteric vein, there is a rapid rise in venous pressure followed by a slower progressive increase. The point of inflection between the rapid and slow phases of the venous pressure increase is considered to equal capillary pressure.

Ra and Rv were estimated as follows:

$$Ra=\frac{SMAP-CP}{MBF}\ mmHg\cdot ml^{-1}\cdot min^{-1}\cdot 100\ g^{-1}$$

$$Rv=\frac{CP-MVP}{MBF}\ mmHg\cdot ml^{-1}\cdot min^{-1}\cdot 100\ g^{-1}$$

Arterial blood was sampled throughout the experiment. The pH (measured by pH/gas analyzer, Corning 175) was maintained at 7.3-7.5 by infusing sodium bicarbonate (1.5%). Body temperature was monitored and maintained at 37±0.5℃ with heating pad and lamp.

Drugs

Vasoconstrictors used were l-noradrenaline bitartrate (Sigma), phenylephrine HCl (Sigma) and l-adrenaline bitartrate (Sigma). Drug solutions were slowly infused with 0.1 ml/100 g body weight through arterial circuit. dl-Propranolol HCl (Sigma) was intraperitoneally administered with a dose of 5 mg/kg once daily and 3 mg/kg three times daily for 10 days.

In all groups of animals, indomethacin HCl(5 mg/kg, Sigma) was administered 30 min prior to experiments. To estimate the vascular reactivity to noradrenaline and adrenaline, propranolol, dl-normetanephrine HCl (Sigma) and desipramine HCl (Ciba-Geigy) were previously administered (1 mg/kg, s.c., each), respectively. In the case of phenylephrine, propranolol (1 mg/kg, s.c.) was injected alone.

Statistical analysis

All values are expressed as the mean±S.E. of mean. Results within groups were compared with Student's t-test. Values of $p<0.05$ were judged to be significant.

RESULTS

Basal hemodynamics

As shown in table 1, SPP of PL group was significantly elevated when compared to that of sham (6.4±0.5 in Sham vs. 12.5±0.3 mmHg, $p<0.001$) in association with increases of MBF (0.21±0.01 in Sham vs. 0.34±0.02 $ml\cdot min^{-1}\cdot 100\ g^{-1}$, $p<0.001$). and CP (12.9±0.5 in Sham vs. 17.6±0.7 mmHg, $p<0.001$). Otherwise, in PL group Ra (160.8±11.1 in Sham vs. 81.1±8.0 $mmHg\cdot ml^{-1}\cdot min^{-1}\cdot 100\ g^{-1}$, $p<0.001$) and Rv (22.6±1.2 in Sham vs. 16.0±0.6 $mmHg\cdot ml^{-1}\cdot min^{-1}\cdot 100\ g^{-1}$, $p<0.001$) were markedly decreased. However, there was shown little difference in the actual levels of SMAP between sham and PL groups.

Vascular reactivity

In the present study, it was aimed to assess the alterations in the vascular reactivities to vasoconstrictors such as noradrenaline (non-specific alpha adrenoceptor agonist), phenylephrine (selective alpha 1-adrenoceptor agonist) and adrenaline (circulating catecholamine). As depicted in Fig. 2, in response to NA(10^{-8}-10^{-4} M), the curves of SMAP and Ra were increased in a dose-dependent manner and those of MBF and CP were in the same manner decreased. However, there were found no differences of the hemodynamic reactivities to NA between PL and sham groups except for Rv, its

Table 1. Steady state actual levels of circulatory hemodynamics in the sham and portal ligated rats

	Sham (n=13)	Portal ligated (n=22)
Splenic pulp pressure (mmHg)	6.4 ± 0.5	12.5 ± 0.3*
Superior mesenteric arterial pressure (mmHg)	46.8 ± 2.6	44.3 ± 2.4
Superior mesenteric venous pressure (mmHg)	8.1 ± 0.4	12.3 ± 0.5*
Mesenteric blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	0.21 ± 0.01	0.34 ± 0.02*
Precapillary resistance ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$)	160.8 ± 11.1	81.1 ± 8.0*
Capillary pressure (mmHg)	12.9 ± 0.5	17.6 ± 0.7*
Postcapillary resistance ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$)	22.6 ± 1.2	16.0 ± 0.6*

Values are expressed as mean ± S.E.M.
n ; numbers of experiments.
*, $p < 0.001$: Significantly different from sham group

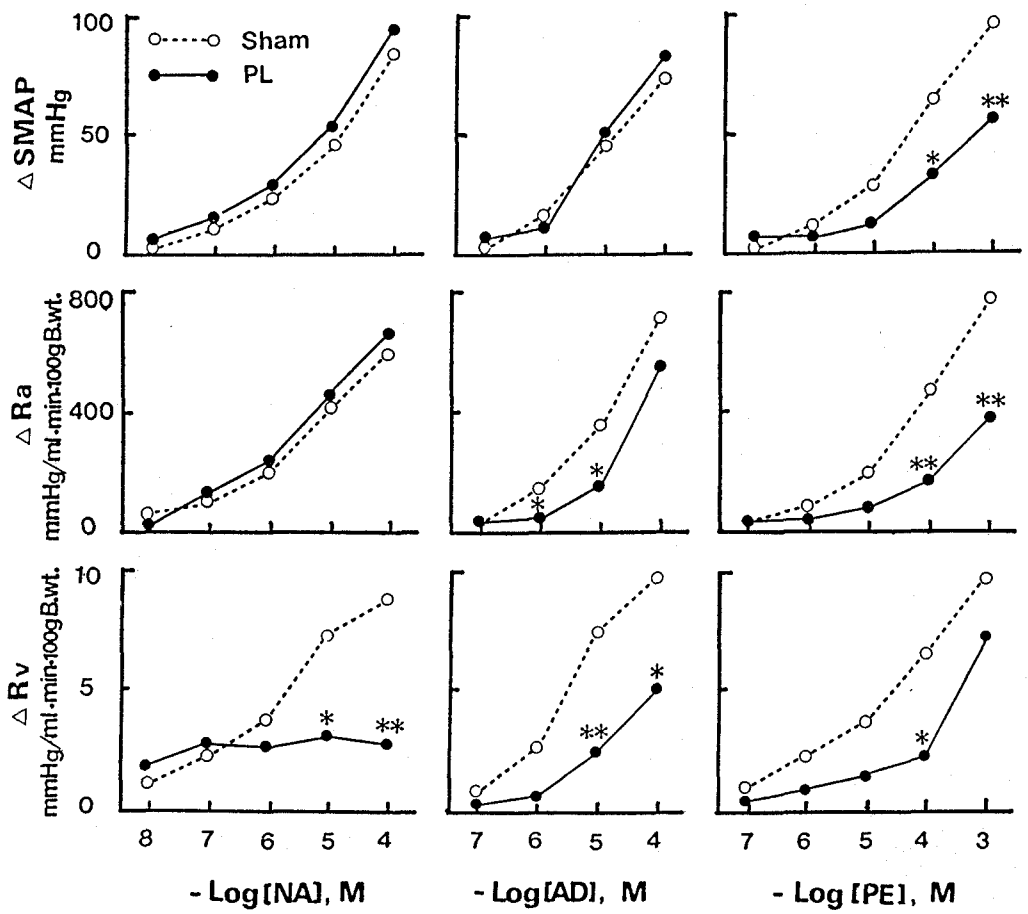

Fig. 2. Comparisons of reactivity to noradrenaline (NA), adrenaline (AD) and phenylephrine (PE) of the circulatory hemodynamics between sham and portal-ligated rats. *, $p < 0.05$; **, $p < 0.01$: Significantly different from sham group.

Table 2. Steady state levels of circulatory hemodynamics in portal ligated rats chronically treated with propranolol[a]

	PPL-1 (n=10)	PPL-3 (n=8)
Superior mesenteric arterial pressure (mmHg)	49.9 ± 1.2	58.9 ± 3.2
Superior mesenteric venous pressure (mmHg)	10.1 ± 0.8	9.6 ± 1.3*
Mesenteric blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	0.31 ± 0.02	0.25 ± 0.01*
Precapillary resistance ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$)	105.2 ± 5.8	174.1 ± 22.3**
Capillary pressure (mmHg)	17.3 ± 0.6	15.5 ± 1.3
Postcapillary resistance ($mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$)	22.9 ± 0.5**	24.2 ± 1.3**

a ; PPL-1 ; Propranolol was administered with a dose of 5 mg/kg i.p., once daily for 10 days. PPL-3 ; Propranolol with a dose of 3mg/kg i.p., three times daily for 10 days.
Values are expressed as mean ± S.E.M.
n ; represents numbers of experiments.
*, $p < 0.02$; **, $p < 0.001$: Significantly different compared with those of PL (see in table 1.).

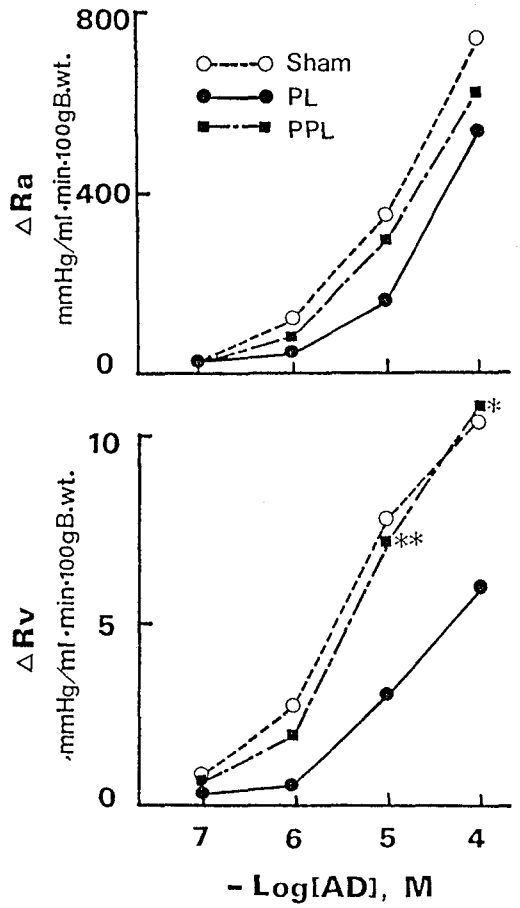

Fig. 3. Effect of longterm treatment with propranolol on the reactivity to adrenaline (AD) in the portal-ligated rats. *, $p < 0.05$; **, $p < 0.001$: Significantly different from portal-ligated rats (PL).

response to NA in PL being drastically attenuated even in the dose of 10^{-5}M NA (8.3±1.9 in Sham vs. 2.9±1.1 $mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$, $p<0.05$) and 10^{-4}M NA (8.7±2.5 in Sham vs. 2.2±0.9 $mmHg \cdot ml^{-1} \cdot min^{-1} \cdot 100\ g^{-1}$, $p<0.05$). Interestingly, in response to adrenaline both Ra and Rv were significantly decreased in PL group without changes in the reactivity of SMAP, MBF and CP. Further, in the case of phenylephrine, SMAP, Ra and Rv responses were concomitantly decreased at relatively higher concentration of phenylephrine.

Effect of propranolol

SMAP and CP of PL group were little affected by chronic pretreatment with propranolol regardless of different methods of administration. In the present study, based on the pharmacokinetics of propranolol, it was administered for 10 days as aforementioned in Materials and Methods. As shown in table 2, in PPL-3 group, decrease in MVP in association with decrease in MBF were observed when compared with those of PL group. The increased CP in PL was slightly decreased in PPL-3. Consequently, both decreased Ra and Rv in PL group were convincingly recovered toward the values of sham group in PPL-3 group. However, Rv is increased by 43.1%($p<0.001$) in PPL-1, differently from PPL-3. Likewise, decreased reactivity of Rv (but not Ra) to adrenaline was effectively recovered toward the values of sham group by propranolol treatment (Fig. 3).

DISCUSSION

In the current experiment, decreases in Ra and Rv with increases in CP and MBF were characteristically observed in association with elevated SPP when measured after 10 days of partial portal stenosis. These results were in good agreement with those reported by Benoit *et al.* (1984) except the Rv which was drastically decreased in our investigation. In contrast to the increment of CP, Ra and Rv in PL group were markedly decreased. Thus, it seems likely that in the PL group the lowered Ra and the increased MBF might cause the CP to rise.

How can the increment in CP be transmitted to the vein and cause sustained portal venous hypertension? One consideration is that the lowered Rv may fully subserve the direct transmission of most of the increased CP to venous part, thereby, readily leading to raise the portal venous pressure. Furthermore, the results obtained from the vascular reactivity studies that the Ra and Rv responses to adrenaline or phenylephrine were parallelly decreased in PL group, additionally indicated to reflect a significant involvement of splanchnic arteriolar dilatation in conjunction with the increase in MBF. In our experiments, MBF was significantly elevated up to 47.8% following portal ligation, the percent increase being stayed between the changes of 41-51% which was measured with microsphere technique by Vorbioff *et al.* (1983).

On the other hand, the reduced reactivity to vasoconstrictors is well consistent with the results demonstrated by Kitano *et al.* (1982) and Kiel *et al.* (1985) that the vascular sensitivity to noradrenaline was reduced in the small intestine and stomach of portal hypertensive rats. Based on these results it is suggested that an altered sympathetic regulation of splanchnic vascular beds may contribute to the increased splanchnic blood flow in portal hypertension (Song *et al.*, 1987).

Kroeger and Groszmann (1985) have examined the effect of propranolol to reduce the elevated portal blood flow through combined participation of beta 1-and beta 2-adrenergic blocking action. Recently, effect of continous propranolol treatment has been focused for treatment of recurrent gastrointestinal bleeding in patients with cirrhosis (Lebrec *et al.*, 1981; Sϕgaard, 1981). However, Burroughs *et al.* (1983) conducted a prospective trial of propranolol for the prevention of recurrent variceal bleeding in 48 patients with cirrhosis of the liver, and observed no significant decrease in rebleeding. Despite of the controversial efficacy in clinical trials, in the present study propranolol treatment with a dose of 3 mg/kg thrice daily for 10 days has characteristically caused increases in the Ra (114.7%) and Rv (51.2%) in assoication with decreases in MBF (26.5%), MVP (22.0%) and CP (11.9%) in the rat with portal hypertension. Furthermore, in vascular reactivity studies the decreased reactivities of Ra and Rv to adrenaline in PL group was effectively reversed by propranolol treatment. In this regard, with the speculations that the alpha adrenoceptors in splanchnic vascular beds are importantly involved in the regulation of circulatory hemodynamics since the different vascular reactivities to different alpha adrenergic agonists were observed in PL group, the effectivenss of propranolol on the Rv can be attributed to the large decrease in MBF in comparison to the change in CP (see PPL-3 group). The ability of propranolol to enhance adrenaline-induced contraction in the mesenteric vasculature of PPL group is considered to have a close relevance to the blockade of beta adrenoceptors located in the mesenteric vascular beds (Cohen and Wiley, 1977).

In conclusion, based on the results of the changes in splanchnic hemodynamics and the reactivities to vasoconstrictors observed in PL and PPL groups, the blockade of beta adrenoceptors of splanchnic vascular beds by propranolol may have a clinical relevance with the effectiveness of longterm treatment with propranolol to reduce recurrent gastointerstinal bleedings in patients with cirrhosis.

ACKNOWLEDGEMENT

We are grateful to Dr. Byung Yong Rhim for his pertinent advice in experiment and to Dr. Oong Suk Yang (Department of Medicine) for his critical review of the manuscript.

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═국문초록═

문맥 고혈압 흰쥐에 있어서 내장혈관의 아드레나린성 수용체의 기능변동과 이에 대한 Propranolol의 효과

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문맥 고혈압 동물에서 내장장기의 혈류역동학적 변동으로서 문맥압의 증가와 동반하여 장간막의 혈류량 증가와 혈관저항의 감소뿐만 아니라 전신 혈관저항의 감소가 특징적으로 야기된다. 문맥고혈압에 있어서 propranolol이 beta 1과 beta 2 수용체의 봉쇄작용으로 문맥고혈압을 저하시킨다는 점에서 사용되기도 한다.

본 실험에서는 흰쥐에서 문맥을 부분적으로 결찰하여 문맥고혈압을 야기하고 10일 후에 내장장기의 혈류역동학적 변동과 혈관 수축성 약물에 대한 반응성의 변동을 관찰하였다. 동시에 이에 대한 propranolol의 효과도 검토하였다. 문맥 결찰 후에는 비 펄프압의 증가와 동반하여 내장장기의 혈류량과 모세혈관압 증가가 야기되었고 동시에 모세혈관 전 저항(Ra)과 모세혈관 후 저항(Rv)은 저하되었다. Noradrenaline에 대한 Rv의 증가반응, adrenaline에 대한 Ra와 Rv의 증가반응, 및 phenylephrine에 대한 상장간막 동맥압, Ra 및 Rv의 증가반응이 특징적으로 문맥결찰군에서 대조군에 비하여 현저히 약화되었다. Propranolol 처치군(PPL-3)에서 장간막 혈류량의 감소가 초래되었고, 문맥결찰군에서 저하된 Ra와 Rv가 propranolol 투여로 대조군 수치로 회복되었다.

이러한 성적의 결과로 문맥 결찰에 의하여 장간막 혈류량 증가와 동반된 Ra와 Rv의 저하는 비 펄프압 증가로 야기된 것으로 추측되며 내장장기 혈류역동학적 및 혈관 반응도의 변동은 장기적인 propranolol 처치로 효과있게 교정되는 점으로 미루어 내장장기의 과혈류역동은 내장장기 혈관의 아드레나린성 수용체의 기능변동과 밀접한 관련이 있다고 사료되었다.