A Possible Antihypertensive Mechanism of Propranolol: Antagonism of Angiotensin II Enhancement of Sympathetic Nerve Transmission Through Prostaglandins

EDWIN K. JACKSON, PH.D., AND WILLIAM B. CAMPBELL, PH.D.

SUMMARY  The effects of propranolol on angiotensin II (All) enhancement of sympathetic nerve transmission were investigated in the in situ blood-perfused mesenteric vascular bed of the rat. Angiotensin II in subpressor concentrations (3 ng/ml) potentiated the vasoconstrictor responses to both sympathetic nerve stimulation (NS) and exogenous norepinephrine (NE). The dl-propranolol had no effect on the basal vasoconstrictor responses to NS and NE, yet inhibited the All-enhanced vasoconstrictor responses to NS by 47% (p < 0.05) and 81% (p < 0.001) at 100 and 300 ng/ml respectively. In contrast, the potentiation of NE responses by All was unaffected by propranolol. A similar blockade of All enhancement of NS was observed with the d-isomer of propranolol. Dibucaine (300 ng/ml), a local anesthetic, failed to alter the basal or All-enhanced responses to either NS or NE. Indomethacin, a prostaglandin synthetase inhibitor (5 mg/kg, s.c.), abolished the inhibitory effect of dl-propranolol on All enhancement of NS. Prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), but not prostaglandin I\textsubscript{2} (PGI\textsubscript{2}), inhibited All enhancement of NS without altering the basal response to NS or NE in indomethacin-pretreated animals. Intraarterial infusions of dl-propranolol, d-propranolol, All, and dl-propranolol-plus-All into the superior mesenteric artery increased mesenteric venous PGE\textsubscript{2} concentrations from 216 ± 33 to 355 ± 33 (p < 0.01), 328 ± 44 (p < 0.05), 325 ± 27 (p < 0.02), and 407 ± 44 pg/ml (p < 0.01) respectively. We conclude that propranolol antagonizes All enhancement of NS by increasing prostaglandin levels in vascular tissue. Furthermore, these findings suggest that propranolol may exert its antihypertensive effect through the release of prostaglandins when used in therapeutic doses in excess of those required for beta-adrenergic blockade. (Hypertension 3: 23-33, 1981)

KEY WORDS  • sympathetic nervous system • angiotensin II • vasoconstriction • norepinephrine • propranolol • dibucaine • indomethacin • prostaglandins • antihypertensive activity

PROPRANOLOL, a beta-adrenergic antagonist, has gained wide acceptance as an antihypertensive drug. Despite this fact, the mechanism by which it exerts its antihypertensive effect still remains unclear. Michelakis and McAllister were the first to report that propranolol lowered plasma renin activity (PRA) in hypertensive patients. Subsequently, Buhler and co-workers reported that administration of propranolol to patients with low, normal, and high renin hypertension resulted in a greater lowering of blood pressure (BP) in those patients with high renin hypertension. Furthermore, they noted that the fall in BP correlated with the suppression of renin release produced by the beta-adrenergic antagonist. From these studies they concluded that beta-adrenergic antagonists lowered BP through suppression of renin release.

It should be mentioned, however, that other investigators have failed to find an association between suppression of renin release and the antihypertensive activity of propranolol. In contrast, Prichard and Gillam as well as Frohlich and co-workers found that the fall in BP with propranolol correlated well with the decrease in heart rate and cardiac output, suggesting that this was the mechanism of the antihypertensive effect. Thus, it would appear that the antihypertensive effect of propranolol in these studies was related to the drug's ability to block beta-adrenergic receptors, whether this be on the kidney or heart.

Esler and co-workers examined the antihypertensive effect of propranolol over a wide range of doses. Propranolol, in plasma concentration between 10-30
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Hypertension was increased, an additional lowering of effect that was unrelated to beta-adrenergic receptor antagonism. In subsequent studies in patients with low, normal, and high renin hypertension, Hollifield et al. observed that BP was significantly and effectively lowered in patients with low renin hypertension if the dose of propranolol was increased. These latter studies would suggest that in higher doses, propranolol exerts an additional antihypertensive effect that may be independent of beta-adrenergic blockade.

In man, the effect of the beta-adrenergic antagonists on the sympathetic nervous system is complex. This is evidenced by the fact that plasma norepinephrine levels have been reported to increase, decrease, or not change following beta-adrenergic blockade.

Nonetheless, a number of studies in animals suggest that, in higher doses, propranolol exerts an additional anti hypertensive action either through a decrease in sympathetic nerve activity via central mechanisms, or adrenergic nerve blockade. Along these lines, we recently have found that propranolol inhibited the ability of angiotensin II to enhance the release of norepinephrine from the adrenergic neuron in doses pharmacologically relevant to the treatment of hypertension. Furthermore, angiotensin II enhancement of norepinephrine release was blocked by beta-selective, beta-selective, and nonselective beta-adrenergic antagonists. The present study was designed to further examine the ability of propranolol to block AII enhancement of norepinephrine release and to ascertain the mechanism by which this blockade occurs.

Methods

Male Sprague-Dawley rats (250-300 g; Simonsen Laboratories) were used in these studies. The animals were maintained on a diet of Wayne Rat Chow and given tap water to drink.

In Situ Blood-Perfused Rat Mesentery

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the mesentery was exposed by a midline incision. In addition, a small incision was made over the trachea to allow tracheotomy. Since the animal was to be subsequently treated with heparin, all incisions were made with electrical cautery. After tracheotomy, the intestines were exteriorized and covered with saline-moistened gauze. The lower abdominal aorta, superior mesenteric artery, and lumbar vein were dissected free from surrounding tissue and silk ties were placed around each. At this point, surgical manipulation was halted for at least 20 minutes to allow total hemostasis before giving 1500 units of heparin via the lumbar vein.

After administration of heparin, the abdominal aorta was cannulated with a 6-inch section of polyethylene tubing (PE 90) which was connected to a 12-inch section of transmission tubing (i.d., 0.045 in.). The transmission tubing was inserted into a Harvard peristaltic pump (Model 1210) and the distal end of the pump tubing was connected to a 1/2 in. section of smaller polyethylene tubing (PE 50). After cannulation of the abdominal aorta, the perfusion line was filled with blood (dead space of perfusion line was 0.8-1.0 ml), and the superior mesenteric artery was cannulated (PE 50). Perfusion of the mesenteric vascular bed was begun at a rate of 2 ml/min by withdrawing blood from the abdominal aorta and pumping it back into the superior mesenteric artery. This blood was recirculated back to the aorta and the pump by the rats' own circulatory system. During the cannulation procedure, the mesenteric vascular bed experienced an ischemic time of only 1–3 minutes.

Next, the mesenteric artery proximal to the cannulation point was severed, as was surrounding tissue, to remove central modulation of mesenteric sympathetic tone. Bipolar platinum electrodes were placed around the mesenteric artery approximately 2 mm distal to the cannulation point. Finally, the abdomen was covered with saline-moistened gauze, and a heat lamp was used to maintain the animal's body temperature. Aortic blood pressure and mesenteric perfusion pressure were monitored with pressure transducers (Narco Model RP-1500) and recorded on a Grass Model 7 Polygraph. Since mesenteric flow was maintained constant by the pump, changes in mesenteric vascular resistance were reflected by changes in perfusion pressure.

The perfusion rate was maintained at 2 ml/min. After an initial vasoconstriction that lasted 10–20 minutes, the baseline mesenteric perfusion pressure stabilized at 54.6 ± 4.3 mm Hg (n = 6) and remained constant throughout the experiment (120 min). Mean arterial pressure of the animal remained stable beginning at 92.5 ± 4.4 mm Hg (n = 6) at time 0 and ending at 96.7 ± 4.8 mm Hg at time 120 minutes with little fluctuation in between.

The sympathetic nerves supplying the mesentery were stimulated via the periradial bipolar platinum electrodes with a Grass Model 54 stimulator for 20 seconds at 3-minute intervals at frequencies from 2 to 7 Hz using 15 V rectangular pulses 1 msec in duration. In preliminary experiments, phentolamine (10 mg/kg, i.v.) or reserpine pretreatment (5 mg/kg, i.p., 24 hours before experiment) abolished responses to periradial nerve stimulation (NS), indicating that vasoconstriction produced by NS was due to activation of sympathetic nerves and not due to direct stimulation of vascular smooth muscle.

Vasoconstrictive responses to exogenous norepinephrine (NE) also were tested. At 3-minute intervals, 30 to 300 ng of NE dissolved in normal saline (10–30 μl) was injected into an injection port located...
proximal to the infusion pump. Responses to NE also were blocked by phentolamine, yet enhanced by pretreatment with reserpine.

Experimental Protocol

Immediately after mesenteric perfusion was begun, infusion of 100 μl/min of normal saline was initiated into the perfusion line with a Harvard infusion pump. After 40 minutes of stabilization, vasoconstrictor responses to NS and NE at several frequencies and doses were obtained. An infusion of one or two of the agents to be tested, dissolved in saline, was then begun at a total infusion rate of 100 μl/min. Drug concentrations are expressed as nanograms of drug per milliliter of mesenteric arterial blood (ng/ml). After 30 minutes, vasoconstrictor responses to NS and NE were repeated. Responses to NS and NE were stable over time (120 min) and were not altered by saline infusion.

Verification that Indomethacin Inhibited Mesenteric Cyclooxygenase Activity

In some experiments, rats were pretreated with indomethacin (5 mg/kg, s.c. in olive oil) 1 hour before control responses to NS and NE were obtained. To verify that mesenteric cyclooxygenase activity was inhibited by this treatment, the response to a 25 μg/ml infusion of sodium arachidonate into the mesenteric artery was determined 1 hour after oil or indomethacin pretreatment. In olive-oil-pretreated animals, arachidonate caused a 40 ± 5.2 mm Hg (n = 4) increase in perfusion pressure. In indomethacin-pretreated animals, the response to arachidonate infusion was inhibited entirely (n = 5). As shown in figure 1, inhibition of cyclooxygenase activity by indomethacin persisted for greater than 2 hours.

Determination of Mesenteric Venous Prostaglandin E₂ Levels

Rats were anesthetized with pentobarbital (50 mg/kg, i.p.), a midline incision made, the intestines exteriorized, and the intestines covered with saline-moistened gauze. A 27-gauge needle and 22-gauge needle were inserted into the superior mesenteric artery and the mesenteric vein respectively. Then 50 μl/min of either saline or saline containing either angiotensin II, dl-propranolol, d-propranolol, or angiotensin II-plus-propranolol was infused into the mesenteric artery with a Harvard infusion pump. After 30 minutes of infusion, 3 ml of mesenteric venous blood was withdrawn from the mesenteric vein into a heparinized syringe on ice. The blood was immediately centrifuged at 4°C, the plasma collected at 4°C and frozen at −20°C until assayed for prostaglandin E₂ (PGE₂) by radioimmunoassay. All samples were assayed within 1 week of collection.

Radioimmunoassay for Prostaglandin E₂

Determination of plasma PGE₂ levels was accomplished by a modification of the radioimmunoassay of Dray and co-workers. Briefly, after adding 1000 CPM of ³H-PGE₂, plasma samples were

![Figure 1](http://hyper.ahajournals.org/)

**Figure 1.** Representative recording demonstrating the inhibition of sodium arachidonate-induced vasoconstriction by indomethacin in the rat mesentery.
acidified to pH 3 with acetic acid, extracted into cyclohexane:ethyl acetate (1:1), and the extract dried under nitrogen. Following reconstitution in benzene:ethyl acetate:methanol:glacial acetic acid (60:40:10:0.0001), samples were subjected to silicic-acid column chromatography and the prostaglandins separated by a benzene:ethyl acetate:methanol solvent system of increasing polarity. The PGE2 fraction was collected, dried under nitrogen, and reconstituted in phosphate-buffered saline containing gelatin. An aliquot of this solution was then assayed for PGE2 by radioimmunoassay utilizing an antibody which cross-reacted 14% with PGE1 and less than 0.4% with PGE2, PGD2, PGF2α, 6-keto-PGF1α, and its 15-keto metabolites. Each sample was corrected for % recovery of 3H-PGE2, which averaged 83%.

Drugs and Chemicals

The drugs and their sources are as follows: dl-propranolol HCl (Ayerst), d-propranolol HCl (Ayerst), norepinephrine HCl (Sigma Chemical), angiotensin II (Beckman), prostaglandin E2 and I2 (Upjohn Company), phenolamine HCl (Ciba), indomethacin (Sigma Chemical), reserpine (Ciba), dibucaine HCl (Ciba), and sodium arachidonate (Sigma Chemical). Doses and concentrations are in terms of the free base. All solvents utilized for assays were of reagent grade and were purified by fractional distillation.

Statistics

Two-tailed unpaired Student’s t tests were used to compare means. In experiments utilizing the in situ mesentery, a control curve and treatment curve for NS and NE were obtained in each animal. However, each animal only received one treatment. Therefore, to compare several treatments, the control curves for each treatment group were combined and the treatment curves were compared to each other and the control curve by analysis of covariance.19

Results

The effects of a 30-minute infusion of dI-propranolol on basal responses to NS and NE are depicted in figure 2. The dl-propranolol (300 ng/ml) did not significantly alter the vasoconstrictor responses to NS or exogenous NE. Thus, at the highest dose of dl-propranolol utilized in this study, adrenergic neuronal blockade was not observed.

Angiotensin II (AII) at 3 ng/ml produced a significant increase in the responses obtained to NS as indicated by the marked elevation of the frequency-response curve (p < 0.001) after AII infusion (fig. 3). This enhancement of adrenergic transmission by AII was inhibited significantly by dl-propranolol in a dose-related fashion. Thus, the enhancement of response by AII was inhibited by 47% at the 100 ng/ml dose of dl-propranolol (p < 0.05) and by 81% at the 300 ng/ml dose (p < 0.001). Furthermore, there was no significant difference observed in the magnitude of control vasoconstrictor responses to NS and those obtained with AII plus dl-propranolol (300 ng/ml).

Angiotensin II also potentiated the response to NE, as indicated by a significant elevation in the NE dose-response curve (p < 0.001) (fig. 3). However, AII potentiated NE responses much less than NS responses. For instance, the normal response to NS at 5 Hz and NE at 100 ng were 18.0 ± 2.3 and 18.8 ± 2.1 mm Hg respectively. Despite these similar responses, AII increased the effect of NS by 24 mm Hg and the
response to NE by only 12 mm Hg. At either 100 or 300 ng/ml, dl-propranolol did not alter the position of the AII-treated NE dose-response curve. Thus, in contrast to the effects of dl-propranolol on AII enhancement of NS, dl-propranolol failed to alter AII enhancement of NE responses.

Since d-propranolol has only one-fortieth the beta-blocking potency of l-propranolol, the effects of d-propranolol on AII enhancement of NS were examined to determine if the inhibition of AII enhancement of NS by dl-propranolol was due to beta-blockade. As shown in figure 4, d-propranolol significantly depressed AII enhancement of NS (p < 0.005) with a potency similar to that of dl-propranolol, indicating that propranolol was not inhibiting AII enhancement by blocking beta-adrenergic receptors.

The local anesthetic action of propranolol is well known. It is possible that any local anesthetic, in equivalent doses, would inhibit AII enhancement of NS. To determine if the effect of propranolol on AII enhancement of NS was due to a local anesthetic action, an attempt was made to inhibit AII enhancement of NS by dibucaine, a local anesthetic more potent than propranolol. As illustrated in figure 5, dibucaine, at a dose equal to the highest dose of propranolol used (300 ng/ml), did not inhibit AII enhancement of NS, and had no effect on AII enhancement of NE (data not shown). Dibucaine at 300 ng/ml had no effect on basal responses to NS or NE, whereas 3 μg/ml of dibucaine severely depressed responses to NS (p < 0.001) (fig. 6). Since dibucaine, a more potent local anesthetic than propranolol, failed to mimic the effects of propranolol, this finding indicated that propranolol was not inhibiting AII enhancement of NS by membrane stabilization.

In 20 experiments, rats were pretreated with the prostaglandin synthesis inhibitor, indomethacin (5 mg/kg, s.c.), 60 minutes prior to obtaining vasoconstrictor responses. This treatment was found to block cyclooxygenase activity in the mesentery for up to 120 minutes (see fig. 1 and Methods). In these

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**Figure 3.** Effects of dl-propranolol on angiotensin II potentiation of sympathetic nerve stimulation (left) and exogenous norepinephrine (right) in normal rats. Points represent mean ± SEM for six rats.

**Figure 4.** Effect of d-propranolol on angiotensin II (AII) enhancement of sympathetic nerve stimulation in normal rats. Points represent mean ± SEM in five rats.
indomethacin-pretreated rats, AII again potentiated the responses to NS, as indicated by an elevation of the frequency-response curve ($p < 0.002$) (fig. 7). Unlike the effect in normal animals, however, propranolol (300 ng/ml) failed to alter AII potentiation of NS in indomethacin-pretreated animals. Thus, there was no difference between the AII-treated frequency-response curves and the AII-plus-propranolol treated frequency-response curves. As in untreated animals, AII had only a modest effect on the responses to NE in indomethacin-pretreated animals (fig. 7).

In the aforementioned experiments, propranolol was found to prevent the enhancement of NS by AII; however, propranolol will also reverse AII enhancement of NS. Figure 8 depicts two representative experiments, one performed in normal animals and the other in indomethacin-pretreated animals. It can be seen that a 45-minute infusion of propranolol completely reversed the enhancement of NS produced by a 15-minute infusion of AII in normal animals but had no effect on AII enhancement in indomethacin-pretreated animals.

Since indomethacin blocks the effects of propranol on AII enhancement of NS, the possibility that propranolol was producing its effect via prostaglandins was examined. Since prostaglandins of the E series are potent inhibitors of norepinephrine release from adrenergic nerve terminals, the effect of prostaglandin $E_2$ on AII enhancement of NS was determined. In indomethacin-pretreated rats, prostaglandin $E_2$ (3 ng/ml) significantly inhibited ($p < 0.05$) the enhanced response to NS elicited by AII (fig. 9), but had no effect on basal responses to.
NS and NE (data not shown). An equal dose of PGI₂ (3 ng/ml) failed to inhibit AII enhancement of NS (fig. 10).

The observations above suggested that propranolol was inhibiting AII potentiation of NS either by causing increased PGE₂ release per se or augmenting AII-stimulated PGE₂ release. To obtain more direct evidence for increased PGE₂ release by propranolol, either saline, AII, dl-propranolol, d-propranolol, or dl-propranolol-plus-angiotensin II was infused directly into the mesenteric artery of rats at a rate sufficient to provide mesenteric arterial blood levels of 3 ng/ml for AII and 300 ng/ml for propranolol. In saline-treated animals, PGE₂ levels in venous blood were 216 ± 33 pg/ml (table 1), similar to the values reported for rat renal venous plasma. Angiotensin II increased venous PGE₂ concentration by 106 pg/ml, while propranolol caused a 139 pg/ml increase above control from 216 ± 33 to 355 ± 33 pg/ml. Interestingly, angiotensin II in combination with propranolol caused an increase in PGE₂ levels by 191 pg/ml, indicating an additive effect with these two agents. Additionally, d-propranolol, like dl-propranolol, increased PGE₂ levels by 109 pg/ml.
Discussion

Angiotensin II potentiates the vasoconstrictor responses to NS and, to a lesser extent, the responses to NE. Propranolol, in a dose-dependent manner, reverses AII enhancement of NS without affecting the basal responses to NS or NE or affecting AII enhancement of NE. This selective reversal indicates that propranolol acts presynaptically since a postsynaptic site of action would reverse the enhancement of both NS and NE. Furthermore, this finding suggests that AII potentiates NS and NE by different mechanisms. Most likely, AII enhances NS by increasing the release of NE, whereas AII enhances exogenous NE by blocking the neuronal reuptake of NE.

As discussed earlier, propranolol, at low concentrations (<30 ng/ml), appears to exert its antihypertensive effect through blockade of renal and/or cardiac beta-adrenergic receptors whereas, at higher concentrations, an additional antihypertensive effect is observed which appears to be unrelated to beta-adrenergic blockade. Since propranolol reverses the potentiation of NS by AII only at concentrations from 100 to 300 ng/ml, it appears that this property of propranolol may correspond to the secondary antihypertensive mechanism and be unrelated to beta-adrenergic blockade. In support of this view, d-propranolol, which has only one-fortieth of the beta-blocking potency of 1-propranolol, also reverses AII enhancement of NS to approximately the same extent as the racemic mixture. Although d-propranolol is
reputed to lack antihypertensive action in humans. Its effect on BP in hypertensive patients has been examined only with doses of d-propranolol that resulted in plasma levels of less than 40 ng/ml. The possibility that higher plasma levels of d-propranolol may lower BP has not been investigated.

Recently, indomethacin was found to interfere with the antihypertensive effect of propranolol in rats, rabbits, and humans. Thus, if inhibition of AIH enhancement of NS is related to the antihypertensive action of propranolol, indomethacin should prevent propranolol from blocking the enhancement of NS due to AIH. Our findings clearly illustrate that indomethacin prevents the effect of propranolol on AIH enhancement of NS. This observation suggests that propranolol is acting through the release of prostaglandins. Along these lines, Ercan reported that PGE2 antagonizes the enhancement of NS by AIH. Using rats in which the endogenous synthesis of prostaglandins is blocked by indomethacin, we also find that PGE2, but not PGD2, reverses the enhancement of NS by AIH in doses that have little effect on basal responses to NS and NE. To further examine the possibility that propranolol acts via a prostaglandin mechanism, experiments were conducted to determine if propranolol alters the release of PGE2 into the mesenteric venous plasma. Propranolol increases the mesenteric venous plasma concentration of PGE2 by 139 pg/ml when infused alone and by 191 pg/ml when infused in combination with AIH. Thus, three lines of evidence suggest that propranolol inhibits AIH potentiation of NS via increased production of prostaglandins: 1) propranolol fails to reverse the enhancement of NS by AIH in animals in which the synthesis of prostaglandins is blocked with indomethacin; 2) prostaglandin E2 mimics the effect of propranolol on AIH enhancement of NS; and 3) propranolol increases PGE2 levels in mesenteric venous plasma when administered alone and in combination with AIH.

Along these lines, even though AIH increases the mesenteric release of PGE2 (table 1), indomethacin fails to alter the degree to which AIH enhances responses to nerve stimulation (fig. 3 vs fig. 7). This lack of an effect with indomethacin suggests that prostaglandins are not involved in the modulation of sympathetic nerve activity at the concentration of AIH used. In contrast, the PGE2 release following combined treatment with AIH and propranolol apparently does inhibit neurotransmission since indomethacin alters the responses following combined infusion of AIH and propranolol. This apparent discrepancy may be due to the site of PGE2 release. Angiotensin II may be releasing PGE2 from a postsynaptic site in the vascular smooth muscle which has limited access to the neuron; therefore, there is little effect on the sympathetic nerve transmission. On the other hand, since propranolol is concentrated 90-fold in neuronal tissue, it may increase intraneuronal PGE2 levels which would effectively inhibit the AIH enhancement of NS. Alternatively, the inhibition of AIH-enhanced responses by PGE2 may require a threshold amount of PGE2 that is not reached by AIH alone, but is attained by the combined effects of AIH and propranolol.

Obviously, the evidence presented is not meant to infer that propranolol is acting only via PGE2. Other prostaglandins, such as PGI2, also may play a contributory role. However, since PGI2 is 700 times less potent than PGE2 in inhibiting adrenergic transmission, propranolol would have to stimulate a disproportionately greater release of PGI2 for this prostaglandin to be of importance. As shown in figure 7, PGI2 at 3 ng/ml has no effect on AIH enhancement of NS, whereas PGE2 at this dose inhibits AIH enhancement of NS.

Since the potentiation of NS by AIH may play a pathophysiologic role in certain types of experimental hypertension, the ability of propranolol to inhibit this effect, via increasing prostaglandin levels, may explain the BP-lowering action of the drug in higher doses. This hypothesis is particularly attractive in light of the recent report that, in the rat, the hypotensive effect of propranolol is blocked by either peripheral sympathectomy or prostaglandin synthesis inhibition. Thus, in this species, an intact adrenergic nervous system and prostaglandin synthesis system are prerequisites for propranolol to exert a hypotensive action. The observation that propranolol increases basal and AIH-stimulated plasma PGE2 levels deserves further attention. Since PGE2 produces vasodilation, increases salt and water excretion, and inhibits norepinephrine release from sympathetic neurons, propranolol-induced increases in PGE2 may explain several pharmacological effects of propranolol that have remained an enigma such as: 1) the ability of propranolol to inhibit AIH potentiation of NS; 2) the additional antihypertensive effect of propranolol seen with doses that are supramaximal with respect to beta-blockade; the decrease in peripheral resistance that occurs during antihypertensive therapy with propranolol; and 4) the interference by indomethacin of the antihypertensive effect of propranolol.

The hypothesis that propranolol may lower BP in hypertensive patients by increasing PGE2 levels is particularly attractive in view of the recent findings that renal PGE2 biosynthesis in human hypertensive states is impaired.
While the present experiments do not address the question of how propranolol increases PGE₂ levels, the increased net production must result from an increased synthesis or a decreased degradation. The major route of PGE₂ degradation is by the enzyme prostaglandin 15-dehydrogenase. Since propranolol does not alter the activity of this enzyme in the rat kidney, it would appear that propranolol does not alter degradation but enhances prostaglandin biosynthesis. The molecular mechanism by which propranolol stimulates PGE₂ synthesis is of considerable interest since its elucidation may present a new approach to antihypertensive drug design.

In conclusion, these studies provide evidence that propranolol increases the net production of PGE₂ in the rat mesentery. This phenomenon may explain how propranolol reverses the enhancement of NS, as well as many of the other pharmacological properties of this drug.

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POSSIBLE ANTIHYPERTENSIVE MECHANISM OF PROPRANOLOL/Jackson and Campbell

33

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E K Jackson and W B Campbell

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