Regulation of Norepinephrine Release from Cardiac Sympathetic Fibers in the Dog by Presynaptic \(\alpha\)- and \(\beta\)-Receptors

NOBUHARU YAMAGUCHI, JACQUES DE CHAMPLAIN, AND RÉGINALD A. NADEAU

SUMMARY The effect of phenoxybenzamine (PBA), desmethylimipramine (DMI), clonidine (CLND), sotalol (STL), and isoproterenol (ISPR) on the release of endogenous norepinephrine (NE) from the heart on right cardioaccelerative nerve stimulation was studied in anesthetized dogs. Under control conditions, the catecholamine levels in coronary sinus blood increased linearly with increasing frequencies of stimulation up to 10 Hz and did not increase further at 30 Hz. The release of NE was markedly enhanced after PBA (1 mg/kg, iv) and DMI (1 mg/kg, iv). The enhanced release of NE after DMI, but not after PBA, was associated with a prolonged response in heart rate. In contrast, NE release was reduced after CLND (15 \(\mu\)g/kg, iv) at stimulation frequencies of 1 and 2 Hz and this was associated with reduced responses in heart rate and left ventricular \(dP/dt\). STL (5 mg/kg, iv) reduced significantly the release of NE at stimulation frequencies of 1–5 Hz, whereas ISPR enhanced NE outflow at frequencies of 1–4 Hz. These results support the existence of both negative and positive feedback mechanisms on the release of norepinephrine by cardiac sympathetic fibers mediated through presynaptic \(\alpha\)- and \(\beta\)-adrenoreceptors, respectively. The functional significance of these mechanisms is also suggested by the correlation found between changes in NE release and variations in cardiac responses under the various drug treatments.

THE MECHANISM of action of phenoxybenzamine and other \(\alpha\)-adrenolytic drugs on the release of norepinephrine (NE) has been studied extensively. Initially, the effect of phenoxybenzamine was attributed either to the blockade of \(\alpha\)-adrenoreceptors in effector organs or to the inhibition of neuronal and extraneuronal uptake of the released amine. However, it has been postulated more recently that the sympathetic nerve terminals may contain \(\alpha\)-adrenoreceptors mediating a feedback mechanism which regulates NE liberation.

Adrenergic blocking agents were found to enhance NE release whereas \(\alpha\)-adrenomimetic drugs, including the released NE itself, were reported to reduce the NE liberation by activating a negative feedback mechanism. However, most of these previous experiments were conducted with tritiated NE on a variety of isolated perfused organs. Furthermore, no attempt has been made to correlate the release of NE with the response of effector organs under these various treatments; therefore the physiological significance of a negative feedback mechanism mediated by presynaptic \(\alpha\)-adrenoreceptors remains obscure.

Little is known of the effects of \(\beta\)-agonists and \(\beta\)-blockers on the release of NE by sympathetic nerve stimulation. Several \(\beta\)-blocking agents have been reported to enhance the release in the isolated rabbit heart. More recently, however, propranolol was shown to reduce the overflow of tritiated NE during sympathetic nerve stimulation in isolated guinea pig atria, suggesting the existence of presynaptic \(\beta\)-adrenoreceptors which would mediate a positive feedback mechanism.

The present study was undertaken to investigate the existence and to evaluate the functional role of these postulated presynaptic \(\alpha\)- and \(\beta\)-regulatory mechanisms of endogenous NE release in vivo.

**Methods**

**PREPARATION OF THE DOGS**

The preparation used in the present study was similar to that used in our previous studies. Thirty-eight mongrel dogs (9.5–17.3 kg) were anesthetized with sodium pentobarbital (35 mg/kg, iv). Artificial respiration was maintained through a tracheal tube with a Harvard pump. A bilateral thoracotomy was performed at the level of the 4th intercostal space, and both vagus nerves were cut in the neck. The coronary sinus and the left femoral artery were cannulated and connected with polyethylene tubes to the left jugular vein and to the distal right femoral artery, respectively. Sodium heparin (200 U/kg) was administered intravenously before the extracorporeal bypasses were opened, and heparin (100 U/kg) was given every 2 hours thereafter.

Aortic pressure, left ventricular pressure and its first derivative \((dP/dt)\), heart rate, mean coronary blood flow in the left anterior descending coronary artery, and a peripheral lead electrocardiogram (AVR) were measured as previously reported and recorded with a Grass polygraph (model 7).

The right cardioaccelerative nerve was stimulated with bipolar platinum electrodes at supramaximal intensity (10 V) for a period of 1 minute (2-msec duration) at various frequencies (0.5–32 Hz) with a Grass stimulator (model S-4). Intervals of 10–15 minutes were kept between each stimulation to allow for the return of cardiac responses to initial levels.
The following drugs were used: phenoxybenzamine hydrochloride (PBA) (Smith, Kline and French), desmethylimipramine hydrochloride (DMI) (Ciba-Geigy), clonidine hydrochloride (CLND) (Boehringer), sotalol hydrochloride (STL) (Mead Johnson), and isoproterenol hydrochloride (ISPR) (Winthrop). After administration of PBA, DMI, CLND, and STL, 20–30 minutes were allowed for their maximum effect before the first stimulation was given. All drugs used in the present study were given intravenously as a bolus injection with the exception of ISPR, which was infused into the left femoral vein by means of a Harvard infusion pump (model 975). All drugs were dissolved in Ringer’s solution and the dose was expressed as the base.

DETERMINATION OF PLASMA CATECHOLAMINES

For measurements of endogenous catecholamine, 3-ml blood samples were collected simultaneously from the coronary sinus and the aorta in about 30 seconds, starting 30 seconds after the onset of stimulation to the end of stimulation.

Plasma catecholamine levels were determined by means of a radiometric enzymatic assay modified by de Champlain et al. The principle of this technique is based on the conversion of NE and epinephrine to tritiated normetanephrine and metanephrine in the presence of catechol o-methyltransferase and tritiated S-adenosylmethionine as a labeled methyl donor. After purification through a series of organic extractions, tritiated normetanephrine was separated from the derivatives of dopamine by oxidation with sodium periodate. Tritiated vanillin thus formed was counted in a Packard liquid scintillation spectrometer. The concentration of plasma catecholamines was calculated from the counts obtained with 0.5 ng of l-norepinephrine (Sigma) which was added to one sample and served as an internal standard.

For statistical evaluation of the difference between various results, means were evaluated by Student’s t-test and by the t-test for paired data when appropriate.

Results

THE EFFECT OF THE RIGHT CARDIOACCELERATOR NERVE STIMULATION ON BASAL PLASMA CATECHOLAMINE LEVELS AND CARDIAC PARAMETERS

The mean catecholamine concentration in coronary sinus blood [0.573 ± 0.082 (SE) ng/ml] obtained from 24 dogs was significantly lower ($P < 0.025$) than that in aortic blood [0.840 ± 0.160 (SE) ng/ml] under basal conditions, in agreement with our previous findings. Control values in both the coronary sinus and in aortic blood sampled 15 minutes after the last cardioaccelerator nerve stimulation were not significantly increased compared to initial values (Table 1). Average values for the mean aortic pressure, heart rate, dP/dt of the left ventricular pressure and mean coronary blood flow measured before and 15 minutes after the stimulations were not statistically different (Table 1). The increase in NE overflow into the coronary sinus was frequency dependent up to 10 Hz but did not increase further at the higher frequency of 30 Hz (Fig. 1). In contrast, circulating catecholamine levels in aortic blood did not change significantly during the period of stimulation at any frequency.

EFFECTS OF DRUGS ON BASAL PLASMA CATECHOLAMINE LEVELS AND CARDIAC PARAMETERS BEFORE SYMPATHETIC NERVE STIMULATION

Basal circulating catecholamine levels and some parameters of cardiac function did not change significantly 30 minutes after the injection of PBA (1 mg/kg, iv) (Table 2). The left ventricular dP/dt and mean coronary blood flow decreased only slightly whereas the mean aortic pressure decreased significantly by about 22% ($P < 0.05$).

Catecholamine levels both in coronary sinus and aortic blood slightly increased after the injection of DMI (1 mg/kg, iv), but this difference was not statistically significant (Table 2). A slight but significant ($P < 0.05$) increase in heart rate and mean coronary blood flow was observed. The mean aortic pressure increased by 11% ($P < 0.001$) after the injection but gradually returned to the control level during the subsequent experimental period.

After the combined administration of DMI and PBA (1 mg/kg iv, each) given at an interval of 2 minutes, the same trends were observed in the catecholamine levels and heart rate as after the administration of DMI alone (Table 2). The left ventricular dP/dt and mean coronary blood flow were unchanged whereas the mean aortic pressure was significantly reduced.

The administration of CLND (15 μg/kg, iv) was accompanied by a significant decrease in catecholamine levels of coronary sinus and aortic blood by more than 70%, 10 minutes after injection (Table 2). These levels were still slightly lower than initial levels at the end of the experiment, but these differences were not significant. Cardio-

### Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before stimulation</th>
<th>After stimulation</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA levels (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary sinus</td>
<td>0.678 ± 0.133</td>
<td>0.872 ± 0.143</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Aorta</td>
<td>1.023 ± 0.231</td>
<td>1.056 ± 0.171</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Mean AP (mm Hg)</td>
<td>92.4 ± 2.9</td>
<td>90.3 ± 3.2</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>129.9 ± 4.9</td>
<td>123.4 ± 5.5</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2563 ± 124</td>
<td>2265 ± 112</td>
<td>24</td>
<td>NS</td>
</tr>
<tr>
<td>Mean CBF (ml/min)</td>
<td>8.4 ± 0.9</td>
<td>7.3 ± 0.9</td>
<td>16</td>
<td>NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± se.

CA = catecholamine; AP = aortic pressure; HR = heart rate; LV = left ventricular; CBF = coronary blood flow; n = number of dogs tested; NS = the absence of significance between values measured before and those measured 15 minutes after stimulation.
The aim of the present study was to verify whether the postulated mechanisms for the regulation of the release of NE mediated through presynaptic α- and β-receptors were functional in vivo. The present results strongly support the

vascular effects of CLND were characterized by a transient but marked increase in the mean aortic pressure and the left ventricular pressure which lasted about 5 minutes and was followed by a decrease in all parameters.

Catecholamine levels in coronary sinus and aortic blood were not significantly decreased after STL (5 mg/kg, iv), but were significantly increased during infusion of ISPR (0.5 μg/kg per min) (Table 3). The mean aortic pressure was not changed, but the values of all the other cardiac parameters were significantly reduced 20 minutes after STL. During the infusion of ISPR, the mean aortic pressure decreased significantly by 31% while the heart rate, the left ventricular dP/dt, and the mean coronary blood flow increased significantly by 32%, 130%, and 145%, respectively. These changes in cardiac function remained relatively stable throughout the infusion.

**EFFECTS OF DRUGS ON THE RELEASE OF NE AND THE RESPONSES OF THE HEART DURING STIMULATION OF THE RIGHT CARDIOACCELERATOR NERVE**

The overflow of NE in coronary sinus blood was significantly enhanced by either PBA or DMI or a combination of both drugs at all frequencies of right cardioaccelerator nerve stimulation (Fig. 2). However, the effect of PBA was greater at low frequencies and lesser at high frequencies compared to the effect of DMI treatment. This difference became clearer when the increase in NE release after either drug treatment was expressed in percentage of increase (Fig. 3). In DMI-treated dogs the injection of PBA increased further the effect on the transmitter release (Fig. 2). After treatment with PBA or DMI or the combination of both, the NE liberation was greater at 30 Hz than at 10 Hz, in contrast to what was observed in the control curve (Fig. 2).

Before treatment, the heart rate, the left ventricular dP/dt, and the mean coronary blood flow were also frequency-dependent up to 10 Hz but these did not increase further at 30 Hz (Fig. 4). Both DMI and PBA did not alter the amplitude of the response of heart rate or mean coronary blood flow but PBA significantly decreased the response of left ventricular dP/dt at 3 and 10 Hz, and DMI significantly increased the dP/dt at various frequencies of stimulation (Fig. 4). The duration of the response of the heart rate, expressed as the half-time of recovery, was not altered by treatment with PBA but was significantly increased after DMI treatment (Fig. 5).

After treatment with CLND, the release of NE was significantly decreased only during stimulation at 1 and 2 Hz but was nevertheless lower at higher frequencies (4–16 Hz) (Fig. 6). When expressed in percentage of decrease, it became obvious that the liberation of NE was inhibited more effectively at lower than at higher frequencies of stimulation following CLND treatment (Fig. 3).

Concomitant with the decrease in NE release, frequency-response curves for heart rate and left ventricular dP/dt were significantly decreased after treatment with CLND at frequencies of 0.5–2 Hz (Fig. 7). The response of the mean coronary blood flow also tended to be inhibited at lower frequencies but these changes were not statistically significant.

As we reported in a previous study, the amount of NE released into the coronary sinus blood could be correlated with the changes in various parameters of heart function in response to right cardioaccelerator nerve stimulation not only before but also after drug treatment. Before treatment, the best correlation was obtained with left ventricular dP/dt (Table 4), in agreement with our previous findings. Correlation coefficients were also found to be highly significant and sometimes better for almost all parameters of cardiac function after treatment with various drugs, especially after CLND treatment.

The release of NE was significantly reduced after STL at stimulation frequencies of 1, 3, and 5 Hz (Fig. 8), whereas in dogs infused with ISPR the liberation was enhanced at 1, 2, and 4 Hz (Fig. 9). After treatment with either STL or ISPR, the transmitter release was altered less at higher frequencies of stimulation (8–32 Hz). When expressed in percent change from the control value, a reciprocal relationship was observed between the effects of STL and ISPR (Fig. 10).

Responses of the heart to right cardioaccelerator nerve stimulation were significantly decreased at all frequencies after the injection of STL, whereas they were only slightly enhanced during the infusion of ISPR (Fig. 11).

**Discussion**

The aim of the present study was to verify whether the postulated mechanisms for the regulation of the release of NE mediated through presynaptic α- and β-receptors were functional in vivo. The present results strongly support the
existence of such positive and negative feedback mechanisms and suggest a physiological role for these presynaptic receptors in the cardiac responses to sympathetic stimulation in the dog.

It is well documented that the release of NE does not increase further and even decreases at frequencies of stimulation above the physiological range. The leveling or decrease in the liberation of the neurotransmitter at 30 Hz was interpreted as being due either to exhaustion of a readily available NE pool or to the occurrence of a local negative feedback mechanism mediated by the action of NE on presynaptic a-receptors. The present study...
FIGURE 2  Frequency-response curves of plasma catecholamine levels in coronary sinus blood in response to various frequencies of right cardioaccelerator nerve stimulation in anesthetized dogs before (control, n = 19) and after administrations of phenoxybenzamine (PBA, n = 6), desmethylimipramine (DMI, n = 7), and a combination of these drugs (DMI + PBA, n = 6). The results are expressed as the increment above each control value taken before stimulation. Each point represents the mean ± SE. The frequency-response curves for lower frequencies is enlarged in the upper portion of the figure. The asterisk indicates the statistical significance compared to values obtained before drug administrations at the level of P < 0.05.

in vivo indicates that the plateau of liberation observed above 10 Hz is not due to the exhaustion of NE stores, because the NE release could be increased by several-fold after treatment with an α-blocker. Furthermore, the administration of an α-blocker increased even more the release of NE in a preparation in which the release already was augmented after blockade of the reuptake mechanism by pretreatment with DMI. Similar observations were also reported by others on isolated organ preparations.18-20

Since a change in the enzymatic degradation or synthesis of the released amine is unlikely to occur under the present experimental conditions, the enhanced release of NE in response to sympathetic nerve stimulation after treatment with PBA could be explained either by inhibition of the uptake mechanism or by blockade of an autoinhibition mechanism mediated through presynaptic α-adrenoceptors.16,17 Several α-adrenolytic drugs were reported to block the neuronal or extraneuronal uptake mechanism at high concentrations.21 However, the dose of PBA used in the present study was below the dose required to block the uptake.4,16,20,21 In studies made in the rat in vivo, the uptake of tritiated NE by the heart was inhibited by 53% (P < 0.001) after the injection of DMI (1 mg/kg, ip), whereas treatment with PBA (1 mg/kg, ip) did not reduce the uptake to any significant extent (unpublished observations). Moreover, the enhanced release after PBA treatment was not accompanied by a change in the duration of the response in heart rate following cardioaccelerator nerve stimulation, whereas the duration of the response was markedly prolonged after DMI treatment. Since the blockade of the uptake mechanism is associated with an increase in the physiological response, the present observations suggest that PBA does not increase the NE release by blocking reuptake.

As observed in the present study, other investigators also have reported that CLND and other α-agonists, including NE itself, reduce the liberation of NE from sympathetic nerve terminals on electrical stimulation.3,4,23 These findings also support the hypothesis of a negative feedback mechanism mediated by presynaptic α-receptors. This mechanism appears to be maximally activated by CLND at lower frequencies, so that no further reduction could be observed at higher frequencies. If such mechanism is functional, the NE output per impulse should be reduced at higher frequencies in the untreated animal. Although coronary sinus blood flow could not be measured precisely during the period of blood sampling in the present preparation, the NE output per impulse could be roughly estimated by correcting for changes in the mean coronary arterial blood flow. In the untreated dog, the NE output decreased at higher frequencies, whereas it remained constant after treatment with CLND. The decreased NE output per impulse at supraphysiological fre-
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The negative feedback mechanism is mainly activated at higher stimulation frequencies. Since CLND has been shown to be competitive with the effect of NE and to be antagonized by either PBA or phentol...

FIGURE 4 Frequency-response curves of heart rate, left ventricular dP/dt, and mean coronary blood flow (CBF) to various frequencies of right cardioaccelerator nerve stimulation before and after drug administration in the same dogs represented in Figure 2. The results are expressed as the increment above the control value taken before stimulation. Each point represents the mean ± SE for the same number of dogs as in Figure 2 except for the study of CBF, in which only four dogs were used for each drug treatment. The asterisk indicates the statistical significance compared to values obtained before drug administration at the P < 0.05 level.

FIGURE 5 Frequency-response curves of the duration of the response in heart rate at various frequencies of right cardioaccelerator nerve stimulation before and after administration of PBA, DMI, and the combination of both. The results are expressed in terms of the half-time of recovery to initial values. Each point represents the mean ± SE for the same number of dogs as given in Figure 2. The asterisk indicates a statistical significance at the level of P < 0.02.

FIGURE 6 Frequency-response curves of the plasma catecholamine levels in coronary sinus blood at various frequencies of right cardioaccelerator nerve stimulation before and after administration of clonidine (CLND), 15 μg/kg, iv. The results are expressed as the increment above each control value taken before stimulations. Each point represents the mean ± SE for five dogs. The frequency-response curves for lower frequencies is enlarged on the right of the figure. The asterisk indicates a statistical significance at the level of P < 0.05.
The initial rise in aortic pressure after the intravenous injection of CLND has been attributed to an increase in peripheral resistance by direct stimulation of vascular α-adrenergic receptors, and the subsequent hypotension was postulated to result from centrally mediated reduction in the spontaneous discharge of peripheral sympathetic nerves. The marked decrease in circulating catecholamine levels observed after CLND could be explained by such a central mechanism. However, the action of CLND on peripheral presynaptic α-receptors, as observed in the present study, also may be an important factor in the reduction of circulating catecholamines and in the hypotensive action of that drug.

**Table 4** Correlation Coefficient (r) Calculated between the Increments of Endogenous Catecholamine Levels in Coronary Sinus Blood (ΔCA) and the Corresponding Cardiac Parameters before and after Various Drug Treatments

<table>
<thead>
<tr>
<th></th>
<th>Before drug (n = 24)</th>
<th>After drug administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBA (n = 6)</td>
<td>DMI (n = 7)</td>
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<tr>
<td>∆CA vs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆HR</td>
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<td></td>
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<tr>
<td>r</td>
<td>0.664</td>
<td>0.001</td>
</tr>
<tr>
<td>P&lt;</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>No. of pts</td>
<td>101</td>
<td>24</td>
</tr>
<tr>
<td>∆LV dP/dt</td>
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<td></td>
</tr>
<tr>
<td>r</td>
<td>0.849</td>
<td>0.001</td>
</tr>
<tr>
<td>P&lt;</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>No. of pts</td>
<td>101</td>
<td>24</td>
</tr>
<tr>
<td>∆Mean CBF*</td>
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<tr>
<td>r</td>
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<td>0.001</td>
</tr>
<tr>
<td>P&lt;</td>
<td>0.1</td>
<td>0.010</td>
</tr>
<tr>
<td>No. of pts</td>
<td>73</td>
<td>16</td>
</tr>
</tbody>
</table>

n = number of dogs used; No. of pts = number of the corresponding points tested; other abbreviations as in Tables 1 and 2.

* The correlation coefficient determined with the mean coronary blood flow was obtained from 16 dogs before drug injections and from four dogs in each group treated with drug.
The inability of either uptake inhibition or \( \alpha \)-adrenergic receptor blockade to potentiate the amplitude in heart rate responses to sympathetic nerve stimulation has been reported by several investigators. In agreement with these previous observations, the present results did not show any significant potentiation in heart rate after administration of either DMI or PBA despite a marked increase in the release of NE. It has been previously postulated that the receptors responding to the NE released by nerve stimulation and those responding to bloodborne catecholamines may be different in terms of accessibility, distribution, or type. The significant potentiation in the left ventricular dP/dt after DMI can be explained by the increased liberation of NE. The failure of PBA to potentiate the left ventricular dP/dt may be due to the hypotensive effect of this drug, since the dP/dt is known to be affected by alterations of arterial pressure. The responses in heart rate and the left ventricular dP/dt were significantly reduced after CLND treatment at lower stimulation frequencies, in agreement with previous findings in vagotomized dogs. It is likely that these reduced cardiac responses resulted from the decreased NE liberation. This possibility is also supported by the improved correlation found between the release of NE and the cardiac response after treatment with CLND. At low doses, propranolol decreased the vasonconstrictor response to low frequency
lumbar sympathetic nerve stimulation in the cat, suggesting a reduction in NE release from the nerve endings.

More recently, it has been shown in isolated guinea pig atria that the release of stimulated NE was reduced during nerve stimulation in the presence of a low concentration of propranolol. Since (+)-propranolol, which lacks β-receptor blocking activity, did not reduce the vasconstrictor response to sympathetic nerve stimulation, and because the concentration used in the latter study did not affect neuronal reuptake or adrenergic prejunctional neurotransmission, it was suggested that the effect of propranolol on transmitter release was related to a specific β-blocking action on presynaptic receptors. In agreement with this hypothesis, the release of endogenous NE was significantly reduced during right cardioaccelerator nerve stimulation at low frequencies by pretreatment with a relatively small dose of STL in the present study. It is likely that the reduced release was due specifically to a β-receptor blocking effect, since STL has little local anesthetic effect or quinidine-like activity at the dose used.

Moreover, the reduced release of NE could not be attributed to the decrease in coronary blood flow, because the release observed at stimulations of 10 and 30 Hz was almost identical to that in control dogs despite the significant decrease in coronary blood flow in the STL-treated dogs. The enhanced NE release observed during the infusion of ISPR in response to right cardioaccelerator nerve stimulation is in agreement with similar findings reported in vitro. Since ISPR does not interfere with the neuronal uptake mechanism, it is likely that this compound would increase the liberation of NE by its β-agonist action.

The effects of both STL and ISPR on the liberation of endogenous NE were found to be more effective within the lower range of stimulation frequencies. The lack of sustained reduction in the transmitter release after STL at higher frequencies can be explained by a competitive displacement, at the β-receptor level, of STL by the larger endogenous NE. This would explain the frequency-dependent increase in NE release which was observed even after STL pretreatment. The results obtained in dogs treated with ISPR suggest that this drug stimulates the presynaptic β-adrenoceptors activating the positive feedback mechanism. The failure of ISPR to increase further the release of NE at the higher stimulation frequencies is probably due to the activation of the negative feedback mechanism mediated by presynaptic α-adrenoceptors.

In conclusion, it appears that PBA increases the release of NE mainly by its α-receptor blocking effect at the presynaptic level, thus inhibiting a negative feedback mechanism, while CLND reduces the release by activating this mechanism through its α-receptor stimulating effect. Moreover, the present study also suggests the existence of a positive feedback mechanism mediated through presynaptic β-adrenoceptors on the sympathetic nerve fibers. The demonstration of these two mechanisms in vivo gives support to their physiological role in the regulation of neurotransmitter release from sympathetic fibers. The actions of drugs such as β-blockers and CLND on these presynaptic mechanisms bring about new insight into understanding their therapeutic effects.

Acknowledgments

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References

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Experiments on cat papillary muscles describe a biphasic effect of hypercapnic acidosis on myocardial contractility. After the Pco₂ of the medium is increased, a decrease in contractility is followed by a spontaneous and partial recovery. This recovery takes place in spite of persistent and severe hypercapnia. Although a participation of catecholamines in the biphasic response to Pco₂ could not be ruled out, the fact that in these previous experiments the biphasic phenomenon appeared to be calcium- and temperature-dependent indicates that other mechanisms are involved in the recovery process. For example, there can be an increased availability of calcium ions. This calcium, derived either from intracellular stores or extracellular fluid, would then be available to overcome a response to calcium depletion at the level of myofilaments, such as might be due to intracellular acidosis.

Although a negative inotropic effect of high Pco₂ on frog ventricle has been established, the transient phenomena described for mammalian myocardium have not been studied in the amphibian heart. Several lines of evidence indicate that excitation-contraction coupling is different in amphibian and mammalian heart tissue. In frog cardiac tissue the sparse and less organized sarcoplasmic reticulum (SR) suggests a possible important role for mitochondria in calcium release and sequestration during the contraction-relaxation cycle, and data provided by voltage clamp and other studies suggest that sources other than SR provide calcium to activate the contractile proteins. For these reasons, toad ventricular muscle was chosen for the present study to further elucidate the mechano-electrical coupling.
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