Acute Effects of Metoprolol on Muscle Sympathetic Activity in Hypertensive Humans

GÖRAN SUNDLOF, M.D., B. GUNNAR WALLIN, M.D., ERLAND STRÖMGREN, M.D., AND CHRISTER NERHED, M.SC.

SUMMARY Recordings of multiunit sympathetic activity were made from muscle branches of the peroneal nerve in eight previously untreated subjects with essential hypertension during intravenous administration of the cardioselective beta-adrenoceptor antagonist, metoprolol. Intraarterial blood pressure and central venous pressure were monitored simultaneously. After metoprolol, heart rate fell and central venous pressure increased in all subjects. Blood pressure increased in some subjects and decreased in others whereas the rate of rise of the systolic pulse wave regularly decreased. Sympathetic activity, discharged in pulse synchronous bursts of action potentials, was quantitated by counting the number of bursts and their amplitudes in the mean voltage neurogram. In all subjects, the average diastole was associated with outflow of more sympathetic impulses after metoprolol than before. Total sympathetic activity (expressed as bursts/min multiplied by mean burst strength) also increased after the drug. The mechanism behind the increase of sympathetic activity may be either a direct central nervous effect or a reflex effect elicited from arterial baroreceptors or cardiac receptors.

KEY WORDS • microelectrode recordings • blood pressure • baroreflexes • beta-receptor antagonists

BETA-ADRENOCEPTOR antagonists are used widely in the treatment of arterial hypertension but their mode of action still remains controversial. For postulated antihypertensive mechanisms, changes in the sympathetic outflow to peripheral blood vessels play a central role. Part of the uncertainty regarding the mode of action is due to the lack of direct information of how beta-adrenoceptor antagonists affect sympathetic activity in humans.

During the last decade, a microelectrode recording technique has been used to study sympathetic outflow in human extremity nerves. Such recordings have shown that sympathetic activity in muscle nerves participates in blood pressure control. The activity consists of pulse synchronous discharges of vasoconstrictor impulses, the outflow of which is modulated by both arterial baroreceptors and low pressure receptors. The discharges occur in parallel in different muscle nerves in arms and legs, and the level is remarkably constant over many months in a given individual, although there are considerable interindividual differences in the amount of resting activity.

The aim of the present investigation was to use this method to record sympathetic outflow to the muscles in patients with previously untreated essential hypertension and study how the activity was influenced by a beta-adrenoceptor antagonist without intrinsic sympathetic activity (metoprolol). The present paper describes results from acute intravenous administration of a single dose of the drug. A subsequent report will deal with the effects of long-term treatment.

Methods

Material

Recordings were made in eight subjects, seven men and one woman, aged 26–51 years, who were admitted to hospital for investigation of mild-to-moderate hypertension. The study was approved by the Ethical Committee of the Medical Faculty of the University of Uppsala, and all subjects gave their informed consent. There were no clinical findings suggestive of secondary hypertension or other diseases, and none of the subjects had previously been on antihypertensive treatment. Except for the trial drug, all subjects were untreated during the investigation. No sedation or anesthesia was given. Before the experiment, cardiac
output was measured by dye dilution technique and found to be within normal range (cardiac index = 2.4 to 4.5 liter/min/m²) in all subjects.

Nerve Recordings
Nerve recordings were made with tungsten microelectrodes with tip diameters of a few microns, which were inserted manually through intact skin into a muscle nerve fascicle in the peroneal nerve at the knee. Small electrode adjustments were made until an optimal position was found for recording sympathetic impulses. After amplification, the nerve signal was fed through a RC integrating network (time constant 0.1 sec) to obtain a mean voltage display of the nerve activity. The analog signals of both original and mean voltage neurograms were stored together with other variables on a 8 channel FM tape recorder (Sangamo Sabre VI). During experiments neural activity was monitored on a storage oscilloscope (Tektronix 549) and a loudspeaker. Details about the technique and evidence for the sympathetic nature of the recorded impulses have been described previously.1 5

Arterial Blood Pressure and Central Venous Pressure (CVP)
Arterial blood pressure and CVP were monitored through catheters in the brachial artery and the right atrium, respectively. Catheters were connected to transducers (EMT 35 and EMT 33, respectively) and coupled to EMT 31 manometers (Siemens-Elema, Ltd.). The upper limit of the frequency response of the arterial pressure recording system was 10 to 15 Hz. The ECG was recorded by surface electrodes on the chest.

Signal Analysis
Mean voltage neurogram, arterial blood pressure, and CVP were displayed from the tape on an ink jet recorder (Mingograph 800, Siemens-Elema, Ltd.). Records were divided into periods of approximately 3 minutes' duration, and for each period (obtained before, during, and after the injection of metoprolol) all pulse synchronous bursts that could be identified by inspection of the mean voltage neurogram were marked and counted. The analog signals of mean voltage neurogram, blood pressure, and CVP were then converted into digital form (sampling frequency, 100 Hz) and fed into a computer (PDP 11/40). In previous recordings of muscle sympathetic activity, a reflex delay was demonstrated between blood pressure and neural events.2 6 Compensation for this delay was made in the computer. For each heart beat the computer determined systolic, diastolic, mean blood pressure, and RR-interval. For each 3-minute period, mean values of these parameters and mean CVP were calculated. In each subject, the computer determined the maximal rate of rise of the systolic pressure wave (dp/dt max) for each heart beat during one 3-minute control period and one period after the end of the injection of metoprolol. For each period, the mean value of dp/dt max was then calculated. Furthermore, in all 3-minute periods, each heart beat associated with a sympathetic burst was marked and as a quantitative measure of the strength of the burst, the computer determined the amplitude of the burst in the mean voltage neurogram. For each 3-minute period, the strength of the sympathetic activity was expressed by the following three measures: bursts/100 heart beats, bursts/min, and mean burst amplitude. For the analysis, diastolic blood pressure was used since the probability of occurrence of a sympathetic burst is related primarily to diastolic blood pressure variations.3 All changes induced by metoprolol took place during the course of the injection, and, therefore, in each patient mean values from all 5 control periods were compared with mean values from all periods after the end of injection (7 to 10 periods).

Biochemical Analyses
Plasma norepinephrine was analyzed by the radioenzymatic method described by Peuler and Johnson.7 Plasma renin activity (PRA) was determined according to Fyhrquist et al.8

Experimental Procedure
Subjects were in a comfortable supine position. Room temperature was 22° to 24°C. A cubital vein and a brachial artery were catheterized for pressure recordings, and the nerve recording electrode was inserted into a peroneal muscle nerve fascicle at the fibular head. When optimal signal-to-noise ratio for sympathetic impulses was obtained, spontaneous activity was recorded during control conditions for 15 minutes. Blood samples for analyses of plasma catecholamines and PRA were drawn, and then metoprolol (0.15 mg/kg body weight) was injected during approximately 15 minutes. After the end of the injection, recordings were continued for 20 to 30 minutes. New blood samples for analyses of plasma norepinephrine and PRA were taken 12 minutes after the end of the injection and in some cases, also at the end of the experiment.

Results

Effects of Metoprolol on Heart Rate, Blood Pressure, and Central Venous Pressure
Effects of metoprolol on heart rate and central venous pressure were similar in all subjects while the effect on arterial blood pressure varied between individuals (table 1). There was a decrease in heart rate (mean 17%, range 11%–25%) which started early during the injection of metoprolol and was completed at the end of the injection. The extent of cardiac slowing was not related to heart rate prior to the injection or to changes of CVP, arterial blood pressure, and norepinephrine concentrations. CVP increased in all subjects (range 1–4 mm Hg), but no relationship was found between the increase and any of the parameters mentioned above. Except for a marked decrease seen in one subject (Subject 2 in table 1), changes of arterial blood pressure were small and inconsistent and were
**TABLE 1. Circulatory Data Before and After Metoprolol**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age, sex</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
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<td>1</td>
<td>26M</td>
<td>145</td>
<td>117</td>
<td>117</td>
<td>122</td>
<td>4 ± 0.2</td>
<td>6 ± 0.2†</td>
<td>61 ± 1</td>
<td>54 ± 1†</td>
<td>306 ± 14</td>
<td>306 ± 11</td>
</tr>
<tr>
<td>2</td>
<td>36F</td>
<td>159</td>
<td>127</td>
<td>136</td>
<td>108</td>
<td>-1 ± 0.3</td>
<td>1 ± 0.2†</td>
<td>83 ± 2</td>
<td>69 ± 2†</td>
<td>398 ± 12</td>
<td>325 ± 12†</td>
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<tr>
<td>3</td>
<td>38M</td>
<td>141</td>
<td>114</td>
<td>146</td>
<td>117</td>
<td>3 ± 0.4</td>
<td>5 ± 0.4†</td>
<td>85 ± 3</td>
<td>73 ± 1†</td>
<td>328 ± 15</td>
<td>300 ± 16†</td>
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<tr>
<td>4</td>
<td>40M</td>
<td>189</td>
<td>146</td>
<td>186</td>
<td>142</td>
<td>1 ± 0.1</td>
<td>2 ± 0.6†</td>
<td>76 ± 1</td>
<td>65 ± 1†</td>
<td>429 ± 12</td>
<td>367 ± 10†</td>
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<tr>
<td>5</td>
<td>41M</td>
<td>203</td>
<td>152</td>
<td>206</td>
<td>153</td>
<td>5†</td>
<td>9†</td>
<td>65 ± 2</td>
<td>51 ± 2†</td>
<td>467 ± 17</td>
<td>422 ± 14†</td>
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<tr>
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<td>43M</td>
<td>142</td>
<td>113</td>
<td>150</td>
<td>118</td>
<td>1‡</td>
<td>4‡</td>
<td>86 ± 1</td>
<td>70 ± 1†</td>
<td>345 ± 11</td>
<td>336 ± 12†</td>
</tr>
<tr>
<td>7</td>
<td>48M</td>
<td>184</td>
<td>139</td>
<td>185</td>
<td>138</td>
<td>2 ± 0.4</td>
<td>5 ± 0.4†</td>
<td>73 ± 1</td>
<td>65 ± 1†</td>
<td>465 ± 13</td>
<td>387 ± 13†</td>
</tr>
<tr>
<td>8</td>
<td>51M</td>
<td>141</td>
<td>106</td>
<td>147</td>
<td>105</td>
<td>1 ± 0.4</td>
<td>3 ± 0.5†</td>
<td>69 ± 2</td>
<td>51 ± 1†</td>
<td>375 ± 12</td>
<td>348 ± 9†</td>
</tr>
</tbody>
</table>

Mean difference: metoprolol vs control

Mean blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2.4†</td>
<td>-12.5†</td>
<td>-40†</td>
</tr>
</tbody>
</table>

Abbreviations: CVP = central venous pressure; dP/dt max = maximal rate of rise of the arterial pressure pulse. Significance of differences tested with Student's t test for unpaired observations (used on individual subjects) or paired observations (whole material). NS = change from control value not significant.

*Change from control value significant at $p < 0.05$ level.
†Change from control value significant at $p < 0.01$ level.
‡Measurements taken manually from the chart.

not related to changes of norepinephrine concentration in plasma. Figure 1 shows segments of original records, figure 2 illustrates the time course of the changes in one subject, and figure 3 and table 1 summarize data from all subjects.

The maximal rate of rise of the systolic pressure wave decreased after injection of metoprolol in all subjects but one, in whom it was unchanged (table 1).

**Effect of Metoprolol on Sympathetic Activity**

The general character of the nerve activity with pulse synchronous bursts of sympathetic action potentials was preserved after injection of metoprolol (fig. 1). During control conditions there were marked interindividual differences in mean burst incidence (range, 37–90 bursts/100 heart beats, 31–63 bursts/min); but in a given individual the level of activity showed fairly
small variations. In all subjects the number of sympathetic bursts/100 heart beats increased during the injection of metoprolol and remained at the new level during the rest of the recording (figs. 1 and 2). Data from all subjects are summarized in figure 3 and table 2. The increase in number of bursts/100 heart beats was inversely correlated to the mean number of bursts/100 heart beats during control conditions, i.e., in subjects with few bursts before the injection the increase was greater than in subjects with many bursts before the injection (fig. 4 A).

As mentioned above, heart rate always decreased after metoprolol and therefore, if sympathetic activity was expressed as bursts/min, the net effect was variable, with the mean number of bursts/min increasing in some subjects and in others decreasing (fig. 3, last column). However, the strength of individual bursts usually increased after metoprolol. If this is taken into account, the total level of nerve activity (expressed as bursts/min multiplied by mean burst amplitude) was found to increase in all patients but one. This is illustrated in figure 4 B, which shows the change in total nerve activity induced by metoprolol. For technical reasons, absolute burst amplitudes cannot be compared among individuals; therefore, figure 4 shows only changes of activity, the control level being set at 100% in all subjects.

**Figure 3.** Individual mean values of diastolic blood pressure, central venous pressure, heart rate, and sympathetic nerve activity before (C) and after (M) injection of metoprolol.
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Table 2. Sympathetic Nerve Activity Before and After Metoprolol

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
<th>Control</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>BURSTS/100 HEART BEATS</td>
<td>Symp. bursts/100 heart beats</td>
<td>Control</td>
<td>Metoprolol</td>
<td>Control</td>
<td>Metoprolol</td>
<td>Control</td>
<td>Metoprolol</td>
<td>Control</td>
</tr>
<tr>
<td>A</td>
<td>Metoprolol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>55 ± 4</td>
<td>70 ± 6†</td>
<td>34 ± 2</td>
<td>38 ± 3†</td>
<td>2.7 ± 0.2</td>
<td>3.2 ± 0.2†</td>
<td>92</td>
<td>122</td>
</tr>
<tr>
<td>2</td>
<td>57 ± 4</td>
<td>82 ± 3†</td>
<td>47 ± 4</td>
<td>56 ± 3†</td>
<td>5.0 ± 0.7</td>
<td>5.0 ± 0.5</td>
<td>235</td>
<td>280</td>
</tr>
<tr>
<td>3</td>
<td>37 ± 4</td>
<td>62 ± 4†</td>
<td>31 ± 3</td>
<td>45 ± 3†</td>
<td>1.3 ± 0.1</td>
<td>1.8 ± 0.2†</td>
<td>40</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>78 ± 5</td>
<td>89 ± 3†</td>
<td>59 ± 3</td>
<td>58 ± 2(NS)</td>
<td>4.7 ± 0.2</td>
<td>5.9 ± 0.5†</td>
<td>277</td>
<td>342</td>
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<tr>
<td>5</td>
<td>71 ± 5</td>
<td>80 ± 6†</td>
<td>47 ± 2</td>
<td>40 ± 2†</td>
<td>4.2 ± 0.1</td>
<td>4.4 ± 1.3(NS)</td>
<td>197</td>
<td>176</td>
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<tr>
<td>6</td>
<td>69 ± 3</td>
<td>83 ± 4†</td>
<td>59 ± 2</td>
<td>58 ± 4(NS)</td>
<td>3.5 ± 0.1</td>
<td>4.7 ± 0.4†</td>
<td>206</td>
<td>273</td>
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<tr>
<td>7</td>
<td>86 ± 4</td>
<td>97 ± 1†</td>
<td>63 ± 3</td>
<td>63 ± 1</td>
<td>3.4 ± 0.2</td>
<td>4.9 ± 0.2†</td>
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<td>309</td>
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<tr>
<td>8</td>
<td>90 ± 5</td>
<td>96 ± 2†</td>
<td>61 ± 3</td>
<td>49 ± 1†</td>
<td>3.5 ± 0.7</td>
<td>5.5 ± 0.9†</td>
<td>214</td>
<td>270</td>
</tr>
</tbody>
</table>

Mean difference:
metoprolol vs control

+14.5† +0.8(NS) +0.9† +46†

*Change from control value significant at p < 0.05 level.
†Change from control value significant at p < 0.01 level.

Relationship Between Changes in Blood Pressure and Sympathetic Activity

In previous studies, beat-to-beat analyses of the relationship between different blood pressure parameters and muscle nerve sympathetic activity have shown that the occurrence of a sympathetic burst (and the amplitude of the burst) is related primarily to the diastolic blood pressure of the heart beat when the burst was initiated.2 Findings were similar in the present study, and the relationships were preserved after metoprolol (mean correlation coefficient for relationship between diastolic blood pressure and bursts/100 heart beats (based on all 3-minute periods) was −0.73 before and −0.67 after metoprolol; corresponding numbers for relationship to burst amplitudes were −0.67 and −0.71, respectively). Quantitatively, however, a given blood pressure value was associated with more sympathetic bursts of higher amplitude after the injection of metoprolol than before. This is illustrated for one subject in figure 5, which is based on all his heart beats before and after metoprolol and shows histograms of bursts/100 heart beats (left) and mean burst amplitudes (right) at different diastolic blood pressures. Results were similar in seven subjects. In the remaining subject (Subject 2 in the tables), there was no clear difference between histograms obtained before and after metoprolol.

The probability of occurrence of a burst depends not only on the diastolic blood pressure of each individual heart beat but also on the direction of an ongoing blood pressure change. Thus, for a given diastolic blood pressure the probability for occurrence of a burst is higher if pressure is falling than if it is in a rising phase.2,9 Also, in this respect findings were similar before and after metoprolol. To quantitate the "directional dependence," each 3-minute period was divided into two fractions, one consisting of heart beats preceded by beats with higher diastolic blood pressure (falling pressure) and one of beats preceded by beats with lower diastolic pressure (rising pressure). In six patients, the two fractions were then compared with respect to burst incidence (two patients had to be excluded for technical reasons). In five subjects, injection of metoprolol caused no significant change of the mean difference in burst incidence between falling and rising pressure, and individual mean values could either increase or decrease. In one subject, the difference showed a significant decrease (p < 0.01).
Biochemical Measurements

Injection of metoprolol did not significantly change plasma concentrations of norepinephrine. PRA before and after metoprolol was compared in five subjects, and in all five there was a decreased activity after metoprolol (average decrease 43%, range 20% to 59%) (table 1). Two subjects were classified as having low renin hypertension (PRA < 1.0 g/liter hr⁻¹); others had normal values. The effect of metoprolol on PRA, hemodynamic, or neural variables showed no correlation to the initial PRA value. In four subjects, PRA was also analyzed at the end of the experiment, and in all four the PRA decrease was maintained.

Discussion

We found that metoprolol induced a decrease of heart rate and an increase of CVP in all subjects, whereas changes of arterial blood pressure and plasma concentrations of norepinephrine were small and variable. PRA was analyzed in five subjects and decreased in all. These results agree with previous observations. The effect of the drug on sympathetic nerve activity has not been studied previously.

Effect on Sympathetic Activity

Although in the present study sympathetic activity was recorded only in peroneal nerves, the results probably apply to other muscle nerves as well, since resting sympathetic outflow to muscles is known to be virtually identical in different extremity nerves. On the other hand, the results cannot be generalized to sympathetic nerves supplying other vascular beds.

We found that the number of sympathetic bursts/100 heart beats and the strength of the bursts increased after metoprolol. The baroreflex modulation of the sympathetic activity implies that bursts correspond to diastolic pressure reductions whereas pauses between successive bursts correspond to systolic pressure waves. Since systolic inhibitions were complete, outflow of impulses will depend partly on heart rate. Therefore, the number of bursts/100 heart beats was used to provide a heart rate independent measure of how often sympathetic outflow occurred in relation to available opportunities for outflow. Both this measure and the strength of the bursts increased, implying that the average diastole was associated with outflow of more sympathetic impulses after the drug than before. However, it is important to realize that this does not necessarily mean an increased muscle vasoconstriction. The response of the vessels depends on the number of sympathetic impulses per unit time. Since the nerve activity is pulse synchronous, this parameter is influenced by heart rate. Even though the number of bursts/100 heart beats always increased, the concomitant heart rate reduction was large enough to reduce the mean number of sympathetic bursts/min in some subjects. However, the net effect nevertheless became an increase of total sympathetic activity in all subjects but one, since the strength of the bursts increased.

The finding of increased sympathetic vasoconstrictor activity in muscle nerves after acute administration of metoprolol provides the first direct evidence in humans that a beta-receptor antagonist induces neurally mediated peripheral vasoconstriction, and excludes the probability that the peripheral effects of the drug are due solely to unopposed alpha receptor stimulation. The result agrees with previous conclusions based on indirect (hemodynamic) data. Both in awake monkeys and hypertensive humans, total peripheral vascular resistance increased after acute administration of beta-adrenoceptor antagonists. The finding was similar for muscle vascular resistance in awake monkeys and for forearm vascular resistance (mainly muscle) in humans.

FIGURE 5. Occurrence (left) and amplitudes (right) of sympathetic bursts in the mean voltage neurogram in relation to diastolic blood pressure before (dotted columns) and after (open columns) injection of metoprolol in one subject. Histograms based on all heart beats and sympathetic bursts before (1323 and 487, respectively) and after (1543 and 958, respectively) injection of metoprolol.
Possible Mechanisms

A number of mechanisms may be responsible for the increase of sympathetic activity observed. One possibility would be reflex influence from intrathoracic "low pressure receptors." In humans, reduction of intrathoracic blood volume by application of subatmospheric pressure around the lower body causes a reduction of CVP, with unloading of the low pressure receptors and increased sympathetic outflow to muscles. This mechanism cannot explain our results since the injection of metoprolol always caused an increase of CVP. Another alternative would be a decreased firing of arterial baroreceptors. If so, the mechanism cannot have been a change of the level of blood pressure since the same blood pressure level was associated with outflow of more sympathetic activity after metoprolol than before. Even if these two alternatives can be excluded, several other mechanisms are possible, and our data provide no information on which is the most likely.

Possible Mechanism: Decreased Arterial Baroreceptor Firing

Arterial baroreceptor firing may also be affected by changes of dynamic blood pressure components, and human muscle sympathetic activity is indeed sensitive to dynamic baroreceptors stimuli. We found no positive evidence that metoprolol changed dynamic baroreflex effects on sympathetic activity (the strength of the activity correlated equally well with diastolic blood pressure variations and was equally dependent on the direction of ongoing blood pressure changes before and after metoprolol). We did find, however, that the rate of rise of the systolic pressure wave decreased after metoprolol. It is unknown whether a reduced rate of rise of the natural systolic pressure wave will increase muscle sympathetic activity, but when arterial baroreceptors are stimulated in animals there is evidence that the rate of rise of sinusoidal pressure variations may influence renal and splanchnic sympathetic activity, blood pressure, and vascular resistance. Therefore, it cannot be excluded that the reduced dp/dt max seen in the present study contributed to the increased sympathetic activity via reduction of arterial baroreceptor firing. Theoretically, it is also difficult to exclude the possibility that the heart rate reduction per se increased the tendency for bursts to occur simply by increasing the interval between systolic baroreceptor inhibitions. In addition, beta receptor antagonists may decrease arterial baroreceptor firing by a direct action on the vessels harboring the receptors (or on the receptors themselves).

Possible Mechanism: Decreased Firing of Cardiac Ventricular Receptors

In animals, stimulation of cardiac ventricular receptors by wall distension evokes bradycardia and vasodilation caused by inhibition of adrenergic vasoconstrictor activity. It has been shown that injection of propranolol reduces afferent discharges from these receptors, and if metoprolol had similar effects in our experiments, it could explain the increased sympathetic drive to muscles.

Possible Mechanism: Direct Effect of Metoprolol on the CNS

Finally, the increased sympathetic activity need not be a reflex effect but could be due to a direct effect of metoprolol on the central nervous system. Beta receptors are present in several regions of the central nervous system; the antagonists pass the blood-brain barrier and propranolol has been found to affect splanchnic and renal sympathetic activity in animals in a manner suggestive of a central action of the drug.

Conclusions

Acute administration of metoprolol increased sympathetic outflow to the vascular bed of skeletal muscle in humans. The underlying cause cannot be determined; it may be a direct central effect or a reflex elicited either from arterial baroreceptors or cardiac ventricular receptors.

Acknowledgment

The authors thank Brita Nederman for skilled technical assistance.

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