Femoral arterial injection of adenosine in humans elevates MSNA via central but not peripheral mechanisms

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**MacLean, D. A., B. Saltin, G. Rådegran, and L. Sinoway.** Femoral arterial injection of adenosine in humans elevates MSNA via central but not peripheral mechanisms. J. Appl. Physiol. 83(4): 1045–1053, 1997.—The purpose of the present study was to examine the effects of femoral arterial injections of adenosine on muscle sympathetic nerve activity (MSNA) under three different conditions. These conditions were adenosine injection alone, adenosine injection after phenylephrine infusion, and adenosine injection distal to a thigh cuff inflated to arrest the circulation. The arterial injection of adenosine alone resulted in a fourfold (255 ± 18 U/min) increase above baseline (73 ± 12 U/min; P < 0.05) in MSNA with an onset latency of 15.8 ± 0.8 s from the time of injection. The systemic infusion of phenylephrine resulted in an increase (P < 0.05) in mean arterial pressure of −10 mmHg and a decrease (P < 0.05) in heart rate of 8–10 beats/min compared with baseline values before phenylephrine infusion. After adenosine injection, the onset latency for the increase in MSNA was delayed to 19.2 ± 2.1 s and the magnitude of increase was attenuated by ~50% (123 ± 20 U/min) compared with adenosine injection alone (P < 0.05). When a cuff was inflated to 220 mmHg to arrest the circulation and adenosine was injected into the leg distal to the inflated cuff, there were no significant changes in MSNA or any of the other measured variables. However, on deflation of the cuff, there was a rapid increase (P < 0.05) in MSNA, with an onset latency of 9.1 ± 0.9 s, and the magnitude of increase (276 ± 28 U/min) was similar to that observed for adenosine alone. These data suggest that ~50% of the effects of exogenously administered adenosine are a result of baroreceptor unloading due to a drop in blood pressure. Furthermore, the finding that adenosine did not directly result in an increase in MSNA while it was trapped in the leg but that it needed to be released into the circulation suggests that adenosine does not directly stimulate thin fiber muscle afferents in the leg of humans. In contrast, it would appear that adenosine exerts its effects via some other chemically sensitive pool of afferents.

**THE EFFECTS OF ADENOSINE INFUSIONS OR INJECTIONS ON CARDIOPULMONARY AND NEUROPHYSIOLOGICAL RESPONSES HAVE BEEN THE FOCUS OF MANY INVESTIGATIONS. IN CONSCIOUS HUMANS, ADENOSINE RESULTS IN AN ELEVATION IN LOCAL BLOOD FLOW, HEART RATE, RESPIRATORY RATE, AND MUSCLE SYMPATHETIC NERVE ACTIVITY (MSNA) (2–4, 6, 7). THE MECHANISM OF ACTION OF INTRA-ARTERIAL INJECTIONS OF ADENOSINE HAS BEEN SUGGESTED TO CONSIST OF THREE COMPONENTS. THE FIRST IS A RESULT OF BARORECEPTOR UNLOADING DUE TO A DROP IN DIASTOLIC BLOOD PRESSURE, THE SECOND IS DUE TO ARTERIAL CHEMORECEPTOR ACTIVATION (2, 3, 25), AND THE THIRD IS THOUGHT TO RESULT FROM MUSCLE AFFERENT ACTIVATION (6, 7).

The effects of adenosine on muscle afferents are of particular interest because it has been suggested that this substance (6) plays an important role in evoking the exercise pressor reflex (15). Costa and Biaggioni (6) injected adenosine into the brachial artery of human subjects and found that MSNA approximately doubled. In a more recent study, the same group (7) repeated the procedure with a pneumatic cuff placed proximal to the injection site and inflated to 50 mmHg to prevent the spillover of adenosine into the systemic circulation. An increase in MSNA was observed that was similar to that observed during handgrip exercise, and prior infusion of theophylline resulted in an attenuation of the MSNA response to exercise. They concluded from these experiments that adenosine activates muscle afferents (presumably group III and IV) and is directly involved in the exercise pressor reflex in humans.

In contrast, Rotto and Kaufman (19) injected adenosine and 2-chloroadenosine into the femoral artery of cats and directly measured the activity of group III and IV muscle afferents. They found that only 15% of the afferents measured were stimulated by adenosine and its analog. These findings directly conflict with those of Costa and Biaggioni (6, 7), and several explanations have been suggested, including species differences, to explain these discrepancies. However, in the study by Costa and Biaggioni (7) a number of other factors may have contributed to the increased MSNA associated with adenosine injection. In their study, the pneumatic cuff was inflated to only 50 mmHg and local venous blood flow was not measured. Therefore, some adenosine may have escaped through the forearm venous circulation and stimulated afferents in other tissue beds. For example, adenosine has been shown to stimulate carotid body chemoreceptors (25) as well as cardiac afferents (8, 9), resulting in sympathetic activation. Therefore, further investigations are needed to positively conclude whether exogenous adenosine directly activates muscle afferents in humans.

Therefore, the aims of the present study were several-fold. First, adenosine was injected into the femoral artery of human subjects to determine the onset latency, time course, and magnitude of the MSNA response. Second, the importance of the baroreflex to sympathetic activation was examined by systematically infusing phenylephrine before adenosine injection. Finally, it was determined whether adenosine directly stimulates thin fiber muscle afferents by injecting adenosine distal to a thigh cuff. The cuff was inflated to 220 mmHg to ensure that adenosine did not reach the systemic circulation while simultaneous Doppler measurements of femoral artery and thigh skin blood flow were made.**
MATERIALS AND METHODS

Subjects

The experimental protocol was approved by the Ethical Committee for the Copenhagen and Frederiksberg Communities, and six healthy male subjects were informed of the purposes and risks of the study; they all gave their informed consent to participate. The subjects were aged 24.6 ± 0.2 yr, weighed 78.6 ± 2.3 kg, and measured 182.7 ± 1.7 cm in height.

Preexperimental Protocol

The subjects reported to the laboratory after an overnight fast, and Teflon catheters were inserted below theinguinal ligament into the two femoral arteries and the right femoral vein. The left arterial catheter was used for the continuous measurement of blood pressure while the right arterial catheter was used for the injection of adenosine. Heart rate and right thigh skin blood flow (laser Doppler) were continuously measured and recorded on a Gould recorder. The subjects rested supine while their left leg was prepared for peroneal nerve recording. The details of this method have been described previously (1, 14, 24), but, briefly, multiunit recordings of sympathetic nerve traffic were obtained by using a tungsten electrode placed in a muscle fascicle within the peroneal nerve. The electrode has a 200-µm shaft that tapers to a 1- to 5-µm tip. A reference electrode was placed in the subcutaneous tissue over the fibular head and 1–3 cm from the active electrode. The neural signal was amplified 1,000 times by a preamplifier and 50–90 times by an amplifier. The resultant signal was fed through a band-pass filter (700 and 2,000 Hz). The signal was rectified and integrated to obtain a mean voltage neurogram.

Experimental Protocols

Protocol 1: Adenosine injection alone (n = 38). The concentration of adenosine needed to elicit an unquestionable increase in MSNA above baseline was determined by injecting variable doses of adenosine (kindly provided by Item Development, Stocksdal, Sweden) into the right femoral artery. The dose necessary varied in the range of 2.5–9 mg, and, once this dose was determined, it was used in all other subsequent protocols. It should be noted that adenosine injection alone (protocol 1) was performed before and after protocols 2 and 3 were conducted to ensure that the effects of adenosine on MSNA still existed and that the peroneal nerve recording site was still viable.

Protocol 2: Adenosine injection after venous phenylephrine infusion (n = 14). In this protocol, phenylephrine was infused into the right femoral vein (0.4–0.6 µg·min⁻¹·kg body wt⁻¹) for several minutes until a steady-state elevation in blood pressure and/or a decrease in both heart rate and MSNA were observed. Adenosine was then injected into the right femoral artery as described in Protocol 1: Adenosine injection alone (n = 38). The rationale for this protocol was that a drop in blood pressure results in an increase in heart rate and MSNA as a result of baroreceptor unloading. Phenylephrine minimizes MSNA responses because of reductions in blood pressure, thereby permitting a more selective evaluation of the effects of adenosine directly on muscle afferents.

Protocol 3: Adenosine injection after thigh cuff inflation (n = 8). In this protocol a cuff was placed around the upper thigh, proximal to the site of adenosine injection, and inflated to 220 mmHg to arrest both the arterial and venous circulation. Approximately 30 s later, adenosine was injected into the right femoral artery, distal to the inflated cuff, and 39.6 ± 2.0 s later the cuff was deflated and the circulation to and from the leg was restored. In each case the cuff was kept inflated for a period of time equal to or greater than the onset latency of the MSNA response to adenosine injection alone. The rationale for this protocol was to trap the injected adenosine in the muscle and determine whether adenosine would activate thin filament afferents directly or whether the MSNA response was mediated via systemic chemoreceptors.

Protocols 4 and 5: Saline infusion and cuff inflation alone. These protocols were used to determine whether the injection process itself or the inflation and deflation of the thigh cuff resulted in any significant change in the measured variables. The injection of saline alone (protocol 4) was always performed first because it was found that after adenosine injection, a saline bolus resulted in a cardiopulmonary effect due to the flushing of residual adenosine in the arterial catheter. Therefore, the saline protocol was performed first, before contamination of the arterial line with adenosine. After this, all other protocols were performed in random order.

Measurement and Analysis

Arterial blood pressure, heart rate (Kone Patient Data Monitor 565A), and MSNA were continuously monitored and recorded on both a Gould recorder and a personal computer. Baseline MSNA was collected for several minutes before the initiation of any protocol, and subsequent protocols were not started until the measured parameters had returned to baseline. The neurogram was analyzed manually by counting the number of bursts and the total burst amplitude. The criteria for an acceptable recording have previously been described in detail (14, 24).

Thigh skin and total lower limb blood flow were determined before and during each protocol by using laser-Doppler (5, 23) and ultrasound-Doppler techniques (11), respectively. Briefly, the laser-Doppler (Periflex 4001 Master) diode (408 Standard Probe) operated with divergent (noncollimated) continuous wave (nonpulsed) light at 780 nm with a maximal emission of 0.8 mW. The ultrasound Doppler (CFM 800) was used to determine the diameter and mean blood velocities of the right femoral artery. An annular phased array transducer probe with an imaging frequency of 7.5 MHz and variable Doppler frequencies of 4.0–6.0 MHz were used in high-pulsed repetition mode (4–36 KHz) to determine vessel diameter and blood flow velocity. All signals were fed to a personal computer for analysis through an eight-channel analog-to-digital converter.

The baseline data before cuff inflation, phenylephrine infusion, and adenosine injection alone were divided into four 15-s blocks. The baseline data after cuff inflation and phenylephrine infusion, but before adenosine injection, were also divided into four 15-s periods. However, for clarity the above baseline data are presented as 1-min time periods. After adenosine injection an onset latency period was identified as the time period from adenosine injection to the point when there was an identifiable increase in MSNA. The time period after the onset latency period was subsequently divided into four 15-s periods and is presented as such.

Statistics

The effects of time and treatment were analyzed by a two-way analysis of variance. If a significant time effect was indicated a Tukey’s (honest significance difference) post hoc test was performed to determine where the significance occurred. Because of the number of time points for each protocol, if a significant treatment effect was indicated, a
Tukey's post hoc test was performed at each time point. Significance was accepted at $P < 0.05$, and the data are presented as means ± SE.

RESULTS

MSNA

The arterial injection of adenosine alone resulted in an elevation of MSNA ($P < 0.05$) with an onset latency of $15.8 \pm 0.8$ s. The increase from baseline in MSNA (Fig. 1) was approximately fourfold and occurred over a 15-s period, as MSNA had returned to baseline after this period. It should be noted that in 42% of the injections a transient decrease in diastolic blood pressure was observed immediately before the onset of the increase in MSNA. Similar increases ($P < 0.05$) were observed in bursts per minute (Fig. 1), bursts per 100 heartbeats, and amplitude per burst, and these changes are depicted in an integrated neurogram in Fig. 1.

The systemic infusion of phenylephrine resulted in an ~50% suppression ($P < 0.05$) of MSNA compared with baseline values before infusion (Fig. 2). A similar

![Fig. 1. Effects of arterial adenosine injection alone on muscle sympathetic nerve activity (MSNA). Injection of adenosine resulted in 4-fold increase in MSNA (A) and 3-fold increase in bursts/min (B) compared with baseline. C: integrated neurogram from 1 subject depicting effects of adenosine. Solid bars, data before adenosine injection; hatched bars, data after adenosine injection. Onset latency period is identified as the time between adenosine injection and the start of increase in MSNA. Note: single dot over spike in neurogram represents recording artifact. *Significant difference from baseline before adenosine injection, $P < 0.05$.](http://jap.physiology.org/Downloadedfrom/10.220.33.1)
decrease (P < 0.05) in bursts per minute was observed after phenylephrine infusion; however, no other differences were observed. Meanwhile, the onset latency for the increase in MSNA was delayed to 19.2 ± 2.1 s (P < 0.05 compared with adenosine injection alone). On adenosine injection, MSNA was increased (P < 0.05), but the magnitude of increase was suppressed (P < 0.05) by ~50% compared with adenosine injection alone. However, the percent increase from the reduced baseline after phenylephrine infusion was similar to that observed for adenosine injection alone. A substantial attenuation (P < 0.05) of both bursts per minute and bursts per 100 heartbeats was also observed compared with adenosine injection alone; however, there were no differences between trials in amplitude per burst. Although phenylephrine infusion resulted in an attenuation of MSNA compared with adenosine injection alone, the increase observed was short lived, with all effects being dissipated after 15 s from the time of onset latency.

The inflation of the thigh muscle cuff before adenosine injection had no effect on MSNA (Fig. 3). After adenosine injection there was no alteration in sympathetic nerve traffic during the 60 s of data collection after the identification of the increase in MSNA. Mean systolic and diastolic blood pressures were calculated by averaging the highest and lowest values during the data-collection periods, and despite the fact that heart rate was increased (which should have increased cardiac output), the arterial injection of adenosine had no effect on systolic, diastolic, or mean arterial pressure.

Heart Rate and Blood Pressure

Adenosine injection alone resulted in an increase (P < 0.05) in heart rate of ~13 beats/min compared with baseline (Table 1) with an onset latency of 9.4 ± 0.7 s. The increase (P < 0.05) in heart rate was sustained throughout the 60 s of data collection after the identification of the increase in MSNA. Mean systolic and diastolic blood pressures were calculated by averaging the highest and lowest values during the data-collection periods, and despite the fact that heart rate was increased (which should have increased cardiac output), the arterial injection of adenosine had no effect on systolic, diastolic, or mean arterial pressure. The systemic infusion of phenylephrine resulted in a decrease (P < 0.05) in heart rate of ~8–10 beats/min compared with baseline before phenylephrine infusion (Table 1). This decrease in heart rate was also lower than that observed for baseline heart rate before adenosine injection alone. Adenosine injection after phenylephrine infusion increased heart rate (P < 0.05) compared with baseline with an onset latency of 9.1 ± 0.8 s, and the magnitude of the increase was similar to that observed for adenosine injection alone. However, unlike the heart rate response observed for adenosine injection alone, the effects of adenosine on heart rate in this protocol were dissipated after 15 s (from the time of onset latency). The infusion of phenylephrine also
resulted in an increase ($P < 0.05$) in systolic and diastolic blood pressure and subsequently mean arterial pressure compared with baseline before phenylephrine infusion (Table 1). These increases in blood pressure persisted throughout the pre- and post-adenosine injection period. The use of the thigh cuff had no effect on heart rate or blood pressure either before or after adenosine injection. After cuff release, heart rate was increased ($P < 0.05$) compared with baseline, with an onset latency of $8.9 \pm 0.5$ s, and the magnitude of the increase was similar to that observed for adenosine injection alone. Similarly, the blood pressure response seen after cuff release was similar to that observed for adenosine injection alone.

Muscle and Skin Blood Flow

The injection of adenosine resulted in an elevation of muscle blood flow, with an onset latency of $7.5 \pm 0.5$ and $8.4 \pm 0.5$ s for adenosine injection alone and phenylephrine infusion plus adenosine injection, respectively. However, after cuff release the onset latency for muscle
DISCUSSION

The major findings of the present study were that femoral arterial injections of adenosine resulted in an elevation in heart rate and MSNA, with an onset latency of 9 and 16 s, respectively. When phenylephrine was infused before the injection of adenosine, the increase in MSNA was attenuated by ~50% and the onset latency was delayed to ~20 s. Furthermore, when a cuff around the thigh was inflated to 220 mmHg and adenosine was injected distal to the restriction, there was no increase in MSNA during the 40 s of cuff inflation. However, on cuff deflation there was a rapid (~9 s) and significant increase in MSNA, which was similar in magnitude to that observed for just adenosine injection alone.

In the present study, femoral arterial injections of adenosine resulted in a three- to fourfold increase in MSNA. These findings are in agreement with but are higher in magnitude than those previously reported (6, 7) and are likely due to the larger doses used in this study as well as the fact that we averaged data over 15-s blocks, whereas the prior studies averaged their MSNA data over 60-s time blocks (6, 7). Traditionally, adenosine has been thought to evoke sympathoexcitation by two mechanisms: 1) baroreceptor unloading due to a drop in diastolic blood pressure (3) and 2) activation of arterial chemoreceptors, specifically in the carotid body. The latter was demonstrated by Watt et al. (25), who reported that ventilation and systolic blood pressure were increased when adenosine was infused proximal to the carotid sinus but had no effect when infused distal to the carotid sinus.

In a series of experiments conducted by Costa and Biaggioni (6, 7), the possible effects of adenosine on muscle metaboreceptors were investigated. In the first set of experiments, adenosine was injected into the brachial artery of human subjects, and a 97% increase in MSNA was noted. They reported that the effects were not due to activation of the carotid chemoreceptors, because the same dose of adenosine given intravenously did not cause any effects. They further ruled out the effects as being caused by local vasodilation, because
relatively long (15.8 s), adenosine injection to the increase in MSNA was similar to that seen during static handgrip. Based on these findings, Costa and Biaggioni concluded that adenosine directly activates muscle afferents in the forearm and contributes to the exercise pressor reflex.

In contrast, Rotto and Kaufman (19) injected adenosine and 2-chloroadenosine into the femoral artery of cats and directly measured the activity of group III and IV muscle afferents, which have receptive fields in the triceps surae muscle. They found that only 15% of the afferents measured were stimulated by adenosine and its analog. Costa and Biaggioni (7) speculated that the discrepancies between their findings and those of Rotto and Kaufman (19) may have been due to species differences, with adenosine being a more impressive metaboreceptor stimulant in humans than in cats. However, data from the present study support the findings of Rotto and Kaufman, and a number of possible factors from each study need to be examined to determine whether adenosine directly stimulates thin fiber muscle afferents.

In the present study, femoral arterial injections of adenosine resulted in substantial sympathetic activation. However, the onset latency from the time of adenosine injection to the increase in MSNA was relatively long (15.8 ± 0.8 s), and Costa and Biaggioni (7) reported a similar onset latency of 17.2 s. For a number of reasons we would have expected a much shorter onset latency if adenosine were a direct stimulant. First, adenosine has a very short half-life (17), and thus its concentration in the limb decreases rapidly. Under these circumstances a direct effect should have occurred sooner. Second, if adenosine were to have a direct local effect, we would have expected a similar onset latency for muscle blood flow (a direct effect) and muscle afferent stimulation. However, the onset latency for MSNA was nearly twice as slow as that seen for muscle blood flow. Finally, prior animal work supports the contention that direct effects should have been seen with a shorter onset latency. For example, rapid arterial injections of lactic acid increased group III discharge within 2 s in the cat triceps surae model (21). Additionally, the infusion of KCl, a potent group III and IV stimulant when infused slowly (15–25 s), evoked an increased discharge with an onset latency of 6 ± 1 s (20). These data do not support the concept that adenosine is a direct muscle afferent stimulant.

In the present study adenosine injection did not result in any significant change in mean arterial pressure, but, in 42% of the injections, a drop in diastolic blood pressure was observed immediately before the onset of the increase in MSNA. Furthermore, when phenylephrine was infused into the femoral vein, heart rate and MSNA were significantly decreased, whereas mean arterial pressure (systolic and diastolic pressure) was significantly elevated. When adenosine was administered under these conditions, the increase in MSNA was attenuated by ~50% and the onset latency was delayed to 19.2 ± 2.1 s. These data suggest that, under normal adenosine administration conditions, the contribution of baroreceptor unloading to the increase in MSNA is at least 50%.

If one-half of the increase in MSNA can be attributed to baroreceptor unloading, then the other one-half must be due to the stimulation of some other chemosensitive pool of afferents. As mentioned previously, Costa and Biaggioni (7) have suggested that these are muscle afferents, on the basis of several key observations. First, they inflated a pneumatic cuff to 50 mmHg proximal to the site of injection, and on adenosine administration they observed an increase in MSNA that was similar to that observed during static handgrip exercise. Second, they infused theophylline (an adenosine-receptor antagonist) before static handgrip exercise, which resulted in an attenuation of the MSNA compared with exercise without theophylline. Although this appears to be strong evidence for direct stimulation of muscle afferents, several points need to be considered. In their pneumatic-cuff experiments, the cuff was inflated to only 50 mmHg and forearm blood flow was not monitored. As a result, it is possible that some adenosine may have leaked out into the systemic circulation and stimulated other chemosensitive afferent beds. In a similar study, Middlekauff et al. (16) injected 2 and 4 mg of adenosine into the brachial artery of humans and observed a 12 and 18% decrease in renal cortical blood flow, respectively. Although these findings are in agreement with ours, Middlekauff and co-workers suggest that sympathetic outflow was increased because of activation of muscle metaboreceptors by adenosine. However, from their study the specific location of these receptors cannot be established, and it is quite possible that afferent beds in tissues other than muscle were responsible for increasing sympathetic outflow. Moreover, it has been estimated that recirculation occurs in as little as 12 s, and thus after injection there is sufficient time for nongraded adenosine to reach other systemic afferent pools.

In the present study, a blood pressure cuff placed around the thigh, proximal to the site of injection, was inflated to 220 mmHg before adenosine injection. When adenosine was injected under these conditions, no increase in MSNA was observed during the 39.6 ± 2.0 s that the cuff was inflated. This duration of time was more than twice the onset latency period observed for adenosine injection alone, and if adenosine was stimulating thin fiber muscle afferents one would expect to see an increase in MSNA after ~16 s or less, yet none was observed. Furthermore, skin blood flow decreased to zero after cuff inflation and remained unchanged after adenosine injection. This observation suggests that adenosine was trapped in the leg and was not leaking out into the circulation. It should be noted that on a number of trials when the cuff was inflated to only...
An interesting finding in the present study was that on cuff deflation after adenosine injection, an increase in MSNA, similar in magnitude to that observed for adenosine injection alone, was observed with an onset latency of only 9.1 ± 0.9 s. These data suggest that, despite a short half-life (17) and being trapped for ~40 s in the leg, there was still enough adenosine present to stimulate carotid chemoreceptors and possibly other chemosensitive afferent beds. Furthermore, these data indicate that the sensitivity of these chemoreceptors to adenosine is high and that a higher dose of administered adenosine may not necessarily result in a greater degree of discharge. Similarly, the much shorter onset latency period observed during this trial is most likely due to the reactive hyperemia associated with cuff release and the subsequent increase in venous return from the leg to the heart. As a result, the adenosine that was present was delivered to other chemosensitive-receptor beds at a greater rate.

This last finding raises an additional point that should be considered. The terminal ends of thin fiber muscle afferents (group III and IV) reside in the interstitial space; thus for adenosine to activate these afferents, a substantial amount must diffuse into the interstitium. It is not known whether this occurs after exogenous adenosine injection, and it is also not known how much the adenosine levels need to rise in the interstitium before afferent activation occurs, if indeed it does occur. It is possible that very little exogenous adenosine administered to the bloodstream ever makes it to the interstitial space of muscle because of the rapid uptake of adenosine by red blood cells as well as by endothelial cells. In fact, the highly efficient nucleoside-uptake of adenosine by red blood cells as well as by endothelial cells. In fact, the highly efficient nucleoside-uptake system (18) of the endothelium may provide a very effective barrier for adenosine transport into the interstitium. This may help to explain the observations reported by Costa and Biaggioni (7), who found that theophylline infusion before static handgrip exercise attenuated the MSNA seen during exercise without theophylline. Under these conditions, theophylline may have blocked the action of endogenous adenosine in stimulating muscle afferents during exercise, since it has been reported that interstitial adenosine levels increase during dynamic exercise (13). Therefore, it is possible that endogenous adenosine stimulates thin fiber muscle afferents that reside in the interstitial space but that exogenously injected adenosine does not. However, to conclusively answer this question, simultaneous measurements of interstitial adenosine and MSNA need to be made during exogenous adenosine injection and endogenous adenosine production.

Because it is unlikely that exogenous adenosine stimulates thin fiber muscle afferents, other mechanisms need to be considered to help explain the increase in MSNA associated with adenosine injection. We have considered the fact that group III afferents, which respond to mechanical disruption of their receptor field, reside in the walls of arterioles. When adenosine is injected into the artery, a substantial concentration gradient is set up on the arterial side of the circulation, and adenosine is known to be a potent vasodilator (10, 22). Therefore, part of the increase in MSNA may be due to rapid vasodilation, resulting in a mechanical disruption of the group III afferent-receptor field. However, this mechanism is not likely for two reasons. First, Costa and Biaggioni (6) demonstrated that nitroprusside given intra-arterially at a dose that evoked the same degree of vasodilation as adenosine had no effect on MSNA. Second, skeletal muscle vasodilation occurred very rapidly in the present study, with an onset latency of 7.5 ± 0.5 s. As a result, it would be expected that MSNA would increase very rapidly with a short onset latency, but this was not observed in the present study. Therefore, any contribution from this mechanism to the increase in MSNA observed in this study by Costa and Biaggioni (6) is highly unlikely.

One other possible mechanism that may contribute to the increase in MSNA activity as a result of adenosine injection is the stimulation of other chemosensitive afferents in other tissues. As mentioned earlier, it has been shown that carotid chemoreceptors are stimulated by adenosine infusion. It has further been demonstrated that adenosine stimulated cardiac afferents (8, 9) as well as renal afferents (12). Because adenosine is such a ubiquitous compound, it is also possible that there are yet-unidentified pools of afferents that are activated by adenosine. Therefore, it is likely that the increase in MSNA observed after adenosine injection, which cannot be attributed to baroreceptor unloading, can be accounted for by stimulation of chemosensitive afferents other than thin fiber muscle afferents.

In summary, this study demonstrates that approximately one-half of the increase in MSNA associated with adenosine injection can be attributed to baroreceptor unloading. Furthermore, adenosine injected into the femoral artery does not directly stimulate thin fiber muscle afferents in the leg of humans. On the other hand, it is most likely that other chemosensitive receptors contribute to the sympathetic activation associated with exogenous adenosine injection. However, our data do not exclude the possibility that endogenously produced adenosine in skeletal muscle activates the sympathetic nervous system via the muscle reflex.

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