Ultraviolet Light May Contribute to Geographic and Racial Blood Pressure Differences

To the Editor:

Dr Rostand’s recent article1 draws attention to a fascinating but hitherto-neglected result of the INTERSALT study: that population mean blood pressures and the incidence of hypertension both appear to be positively correlated with the latitude north or south of the equator at which the population lives. Dr Rostand notes that geographical movement away from the equator is associated with a fall in ambient ultraviolet radiation. Decreased ultraviolet radiation reduces vitamin D synthesis, and this can elevate parathyroid hormone levels; furthermore, parathyroid hormone can stimulate vascular wall growth. Drawing from these data and published evidence for altered calcium homeostasis in human hypertensive subjects, Rostand postulates that the variation in blood pressure with latitude may therefore be linked to the different intensities of ambient ultraviolet light.

Dr Rostand’s proposal is an attractive one, serving as it does to pull together many disparate strands of the complex fabric that seems to underlie the genesis of essential hypertension. It has important potential implications for our interpretation of the role of calcium in hypertension and may offer valuable clues to the understanding of racial differences in salt sensitivity and renin profiles and of different racial susceptibilities to high blood pressure.

There is, however, an additional mechanism by which ambient electromagnetic radiation may reduce blood pressure. Robert Furchgott and his colleagues noted as long ago as 1961 that exposure to light relaxed isolated arterial preparations, although other types of smooth muscle tissue were much less sensitive.1 The vascular photorelaxation was wavelength dependent, increasing as wavelength was reduced from the visible into the ultraviolet range and peaking at around 310 nm. In later experiments, Furchgott’s group found that photorelaxation involved an increase in muscle cell cyclic GMP and that it was independent of the endothelium.2

As far as I am aware, Furchgott did not suggest on the basis of his work that ambient light intensity might affect the vasculature in vivo. Nonetheless, ultraviolet radiation can penetrate deep enough into skin to reach the microvessels, and the cutaneous circulation represents the site of a substantial proportion of total peripheral resistance. Although sympathetic tone has the most dramatic controlling influence on cutaneous vascular flow, it is not unreasonable to imagine that resting cutaneous vascular tone may under some circumstances also be tonically reduced by absorbed ultraviolet radiation. Withdrawal of this dilator effect when exposed for direct photorelaxation of vessels to play an important role is blood pressure regulation. However, there may be sufficient cutaneous exposure to UV light to modulate vascular tone through alterations in vitamin D, parathyroid hormone, and calcium status. Cutaneous vasodilatation in response to UV light exposure is known to result from direct photorelaxation of cutaneous arterioles produced by UV penetration of the skin. It should be noted, however, that not all smooth muscle responds to photostimulation1 and there have been no studies performed on small peripheral resistance vessels. Moreover, because most of the human body is protected from sunlight by clothing, it seems unlikely that sufficient body surface area is exposed for direct photorelaxation of vessels to play an important role is blood pressure regulation. Therefore, there may be sufficient cutaneous exposure to UV light to modulate vascular tone through alteration in vitamin D, parathyroid hormone, and calcium status. Cutaneous vasodilatation in response to sunlight exposure in humans may be more a thermoregulatory response to heat rather than an effect of UV light. Nevertheless, the idea presented by Bell is intriguing and readily testable.

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References


Central Nervous System Is Not Involved in Initiation of the Pressor Effect of 7-Nitroindazole in Urethane-Anesthetized Rats

To the Editor:

We read with interest the article by Sander et al1; it provided a valuable update on the controversies concerning the role of the
inhibition of neuronal nitric oxide synthase (NOS) acting within the central sympathetic nervous system (CNS) in the systemic hypertension caused by NOS inhibition. Some authors have suggested that neuronal NO is involved in the tonic restraint of sympathetic vasoconstrictor outflow from the CNS. Removal of such restraint by inhibition of neuronal NO should, in principle, lead to sympathetic activation and increased systemic blood pressure. After careful analysis of published studies in this area and their own work, Sander et al concluded that central inhibition of NOS does not contribute to the onset of hypertension after systemic NOS inhibition in conscious animals, but it does contribute to the long-term maintenance of such hypertension in conscious rats. Sander et al noted that support for a neurogenic component in NOS–induced hypertension was, however, evident in studies of anesthetized animals. The authors did not clarify whether this effect was on initiation or maintenance of hypertension or both. Some studies in anesthetized rats that were not noted by Sander et al, however, did not support a neurogenic component in the hypertension induced by l-arginine–derived NOS inhibitors.2–4 On the other hand, the rapid pressor effect of diphenyleneiodonium, an NOS inhibitor that is chemically distinct from N6–substituted arginine analogs, does appear to be CNS–dependent in anesthetized rats.5 The basis of these conflicting data on the role of a neurogenic component in NOS inhibition–mediated hypertension in anesthetized animals is unclear.

One way to more specifically assess the contribution of centrally acting neurally derived NO to systemic hypertension is to use NOS inhibitors that do not affect the endothelial isoform of NOS. 7-Nitroindazole has been proposed to be a relatively selective inhibitor for the neuronal isoform of NOS,6 and we believed it might be especially useful in evaluating the specific role of neuronal NO in regulation of arterial blood pressure. We and others have found that 7-nitroindazole induces a moderate pressor effect in unanesthetized as well as urethane-anesthetized rats that achieves a maximal level after 10 to 15 minutes and is maintained unchanged for a subsequent 45 minutes.7 Various factors (eg, use of volatile anesthetics or barbiturates that blunt NO-dependent vasoresponsiveness and hypertension)8,9 may have obscured the moderate pressor effect of 7-nitroindazole in many other studies (for discussion, see Reference 7). The evident rapid pressor effect of 7-nitroindazole in conscious or urethane–anesthetized rats could be the result of inhibition of neuronal NOS in the CNS, leading to a consequent increase in central sympathetic drive.

To test this hypothesis, 11 Sprague-Dawley rats were anesthetized with urethane (1.5 g/kg IP) and artificially ventilated, with blood gas parameters kept within a normal range. Temperature was kept constant at 37°C. Arterial blood pressure was measured through the femoral artery using a blood pressure analyzer (BRP-100, Micro-Med). 7-Nitroindazole dissolved in peanut oil was administered intraperitoneally in a maximally effective dose (50 mg/kg IP) in 5 intact rats and in 5 rats 20 to 25 minutes after the spinal cord was pithed with a metallic rod inserted through the right orbit. Mean arterial blood pressure decreased to 56±6 mm Hg after pithing prior to 7-nitroindazole administration, whereas it was 79±6 mm Hg in the intact rats. In all rats, 7-nitroindazole evoked a prominent pressor effect by 10 minutes after administration. In pithed rats, the mean±SEM of the 7-nitroindazole–induced increase in arterial pressure (15±3 mm Hg) at 10 minutes was not significantly different from the mean of the increase in arterial blood pressure in intact rats (18±3 mm Hg). The pressor effect of 7-nitroindazole was dramatically potentiated (39 mm Hg) in 1 additional pithed rat in which arterial blood pressure was elevated to a normal level by intravenous infusion of epinephrine. A similar potentiation effect of epinephrine on the increase in arterial blood pressure induced by N6–substituted analogs of l-arginine has been reported in pithed, ganglion–blocked, or sympathectomized rats.2–4

Our results therefore suggest that a mechanism other than inhibition of the neuronal NOS in the CNS is responsible for the initial pressor effect of 7-nitroindazole. Thus, the conclusion discussed by Sander et al that a central neurogenic component may not be involved in the initiation of the hypertension after inhibition of NO production is not limited to N6–substituted analogs of l-arginine and can be extended to other classes of NOS inhibitors. It is also important that this conclusion may be valid not only for conscious but also for anesthetized rats, although more detailed studies of anesthetized rats are needed on this point.

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Response:

In replying to the letter by Zagvazdin et al regarding our recent article, we would like to address two issues: (1) the relative contributions of anesthetized versus conscious animal studies and (2) the specificity of indazoles versus methyl arginines as inhibitors of NOS I, the “neuronal” isoform.

First, studies in anesthetized rather than conscious animals provided the initial evidence that a neurogenic component contributes to the blood pressure–raising effect of methyl-arginine inhibitors of NOS. To test this hypothesis, we used conscious unrestrained rats to avoid the potentially confounding effects of centrally acting general anesthetic agents (as exemplified by the noted controversy in this literature). Our results suggest that in addition to differing effects of general anesthetics, differences in
the time course of NO inhibition also account for some of the seemingly contradictory findings in previous studies.

Second, the new data presented by Zagvazdin et al are based on the use of indazole derivatives. These compounds at first were touted as specific inhibitors of NOS I, whereas methyl arginines such as N\(^{\text{a}}\)-nitro-L-arginine methyl ester (L-NAME) are considered promiscuous inhibitors of all NOS isoforms. When administered systemically, the indazoles were found to inhibit NO production in brain, but they caused little or no increase in blood pressure. Subsequently, however, Zagvazdin et al showed that 7-nitroindazole administered intraperitoneally causes a reproducible increase in blood pressure in both urethane-anesthetized and conscious rats. Furthermore, a greater specificity of indazoles versus methyl arginines for inhibition of NOS I over NOS III has not been substantiated by careful kinetic studies of enzymatic activity in vitro, and they were shown to cause relaxation of vascular smooth muscle by mechanisms that do not involve NO. This vasodilatory effect may contribute to the smaller blood pressure-raising effect of 7-nitroindazole relative to the methyl arginines. In designing experiments to test our hypothesis, we interpreted these data to suggest no clear advantages in using nitroindazoles over methyl arginines to test our hypothesis. Indeed, another recent study shows that prolonged oral administration of 7-nitroindazole to conscious rats for 4 weeks resulted in a progressive increase in blood pressure, which parallels our findings using L-NAME. A recent report suggests that newer indazole constructs may have enhanced specificity for inhibition of NOS I. However, even if this is the case, their use may not fully elucidate the role of neurally derived versus endothelially derived NO. NOS I is not purely “neuronal” because it is abundantly expressed in mammalian skeletal muscle, and NOS III is not purely “endothelial” because it is expressed in neurons, where it appears to contribute importantly to neuronal signaling, such as that involved in long-term potentiation.

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Renal Effects of Endothelin-1 in Essential Hypertension

To the Editor

In their recent article, Dr Kaasjager and colleagues reported important data on the renal hemodynamic effects of endothelin-1 (ET-1) in 9 subjects with essential hypertension. They showed that ET-1 elicits a potent vasoconstrictor effect, which was found to be prominent in the renal vascular bed. The authors also showed that treatment with both the angiotensin-converting enzyme inhibitor enalapril and the dihydropyridine calcium channel blocker nifedipine could prevent the effects of ET-1 on systemic blood pressure, although only nifedipine seems to be effective in attenuating the renal constrictor effects of ET-1.

Of interest, the authors measured the ET-1–induced changes of plasma renin activity (PRA) and plasma aldosterone levels but failed to detect any significant effect and thereby excluded that these hormones might account for their renal hemodynamic findings. In fact, contrary to what Kaasjager et al state, ET-1 infusion did induce a consistent 10% increase of plasma aldosterone both when administered alone (in the Control Study) and during enalapril or nifedipine treatment. This increase was significant even though the peptide was infused for only 180 minutes and at a dosage that produced a peak plasma concentration of immunoreactive ET-1 (11.6 ± 1.0 pmol/L) which was subthreshold, ie, lower than the 30 to 300 pmol/L needed to elicit a vasoconstrictor response in various smooth muscle preparations in vitro.

Because ET-1 was shown to enhance aldosterone secretion in different species, including humans, by acting on specific receptors (see Reference 5 for review), in our opinion this finding deserves careful consideration. From the measure of spread (SEM) given with the data, a wide dispersion of the values (corresponding to a variation coefficient ranging between 50% and 60%) is readily evident. This suggests either a large interindividual variability of the plasma aldosterone value or a poor measurement reproducibility, or both. Unfortunately, no information on the method used or on the exact timing of aldosterone measurements is provided in the article; therefore, the questions on methodological accuracy and time course–related variability of plasma aldosterone remain unanswered. Furthermore, it is our general experience that PRA and plasma aldosterone levels do not follow a normal distribution. It is therefore unclear why, although the authors correctly used a logarithmic transformation of the PRA data, they did not do the same for plasma aldosterone values.

We suspect that a more accurate measurement of plasma aldosterone, a larger sample size, and a more appropriate analysis of the aldosterone data could have revealed a statistically significant secretagogue effect of ET-1 on aldosterone. In our view, this is not a trivial issue, since this secretagogue effect of ET-1 in human adrenocortical cells involves a calcium-dependent mechanism. It is thus conceivable that the 1.5-fold higher baseline sodium excretion with a “long-
term” effect of nifedipine. We put forward the alternative hypothesis that this “long-term” natriuretic effect relies in part on the ability of the dihydropyridine calcium entry blockers to interfere with ET-1–mediated aldosterone regulation and thus with the sodium-retaining action of the steroid at the distal tubule. This interpretation accords well with the concept that the natriuretic effect of the dihydropyridine calcium entry blockers occurs even without alterations in renal plasma flow and glomerular filtration rate, i.e., through a tubular mechanism, which mainly involves the fractional distal escape of sodium.

Of further interest is the fact that the authors failed to observe any initial vasodilation in response to ET-1 infusion. They suggest that the ET-1–induced transient vasodilation, which is mainly due to nitric oxide (NO) release mediated via ET₁ receptors on endothelial cells, can be restricted to certain vascular beds and does not involve the renal vasculature. Although we cannot rule out this possibility, it is worth mentioning that (1) an impaired endothelium-dependent relaxation has repeatedly been observed in hypertensive subjects, (2) with immunohistochemistry and reverse transcription–polymerase chain reaction we recently detected ET₄ receptors in vascular smooth muscle cells of the tunica media of human renal arteries obtained ex vivo, and (3) these receptors are likely to mediate for vasoconstriction, at least in certain vascular beds. Thus, it does not seem unreasonable to assume that an endothelial dysfunction, which precedes the onset of clinical signs of renal damage and involves the ET₁-receptor NO release, already exists in the essential hypertensive subjects investigated by Dr Kaasjager and colleagues, as suggested by their own data with l-arginine administration. Alternatively, it might be that the direct ET₁-receptor NO release is masked by a direct vasoconstrictor effect occurring through both ET₄ and ET₃ receptors, which we have found in the tunica media of the human renal vessels.

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Response:

Dr. Rossi and colleagues suggest an alternative explanation of the antinatriuretic effects of ET-1 infusion through its secretory effects on plasma aldosterone levels. Their hypothesis is certainly of interest. However, we feel that from our data this interpretation cannot be supported. First, the difference in plasma aldosterone, which was measured immediately before and at the end of the ET-1 infusion, was not significant. If we use a logarithmic transformation, the increments become even smaller (270 to 288 pmol/L for control; 256 to 267 pmol/L for enalapril; and 270 to 284 pmol/L for nifedipine). The within-assay variance coefficient of our assay was 9%, and the between-assay variance coefficient was 14%. The absence of an effect of pathophysiological increments in plasma ET-1 on aldosterone is in agreement with observations from other groups using similar infusion protocols. Moreover, to really identify the magnitude of a change in plasma aldosterone from our study, one would need a time-control study because there are important diurnal changes in the secretion of the hormone. Second, there was an immediate decrease in sodium excretion after ET-1 infusion, whereas one would expect a delay in the onset of the antinatriuretic effect if it were secondary to aldosterone stimulation. Finally, from our data there are no indications that effects of ET-1 on aldosterone can be modulated by calcium channel blockade.

Rossi et al. also offer an alternative explanation for some of our hemodynamic findings, i.e., the absence of initial vasodilation in response to ET-1 infusion. Although we cannot exclude that impaired endothelium–dependent relaxation could contribute to this phenomenon in these hypertensive subjects, we also did not see this initial vasodilation in previous studies in healthy volunteers, who are assumed to have normal endothelial function. Moreover, we recently performed a study in healthy subjects in whom we infused ET-3, a relatively selective ET₄ agonist. In this study we did not see any vasodilation or vasoconstriction in the kidney despite a threefold increase in plasma ET-3 levels, suggesting that the renal effects of exogenously administered ET-1 in the human kidney are predominantly mediated through ET₄ receptors.

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