Salt-sensitive hypertension in rodents has been associated now for many years with activation of the endothelin (ET) system. This has been reported in doxycorticosterone-salt hypertensive rats and in genetic forms of hypertension, such as the Dahl salt-sensitive rat. However, the involvement of the ET system, as demonstrated by elevation of plasma levels of ET-1, increased tissue concentration of ET-1, or blood pressure—lowering effects of ET antagonists, has been shown when hypertension, often severe, was well established. The same has been suggested for humans, in whom evidence that the ET system was activated was found mostly in stage 2 hypertension, and particularly in subjects with salt-sensitive hypertension, such as blacks. This has been further affirmed by the recent DORADO (darusentan in resistant hypertension) Trial in resistant hypertension in humans, with a favorable response to an ET\textsubscript{A} selective receptor blocker. However, there have been reports of effective BP lowering by ET blockade in stage 1 hypertension. Moreover, a role of the ET system was already described a few years ago in children of hypertensive parents, in whom mental stress evoked a pressor response that was associated with an elevation of circulating ET immunoreactivity.

In the current issue of Hypertension, D’Angelo et al\textsuperscript{9} report the effects of a form of acute behavioral stress, an acute air jet stress, on the pressor response to this stressor in prehypertensive Dahl salt-sensitive rats. The authors find an elevation of circulating catecholamines and ET-1 immunoreactivity, as well as an increase in a marker of oxidative stress (plasma 8-isoprostane). Antioxidant treatment with the superoxide dismutase mimetic Tempol did not lower catecholamines or ET-1 in plasma but suppressed the pressor response and the increase in plasma 8-isoprostane. Administration of an ET\textsubscript{A} receptor antagonist did not affect the pressor response, but a dual ET\textsubscript{A/B} receptor antagonist effectively abrogated both the pressor effect and the elevation of plasma 8-isoprostane. The authors conclude that acute behavioral stress-induced pressor responses in prehypertensive Dahl salt-sensitive rats are mediated by ET-1 acting either solely via the ET\textsubscript{B} receptor or through an interaction with both ET\textsubscript{A} and ET\textsubscript{B} receptors.

Although the experiments performed by D’Angelo et al\textsuperscript{9} are elegant, some questions remain unanswered. Where is the stimulation of ET-1 occurring (Figure)? Is this increase in circulating ET-1 of posterior pituitary origin? In cases of postural hypotension, which are associated with increases in ET-1 on upright tilt, the surge in ET-1 in the circulation has been identified as originating in the posterior pituitary, as shown by its absence in subjects experiencing diabetes insipidus and, accordingly, neurohypophyseal deficiency of antidiuretic hormone (vasopressin). Vasopressin can be released in response to stress stimuli by the neurohypophysis and has been shown to stimulate ET-1 secretion by the endothelium. What is the role of the sympathetic nervous system in the response mediated by ET-1? Is ET-1 released by nerve endings participating in this response? Although Tempol significantly reduced the stress-induced increase in plasma epinephrine, Tempol paradoxically augmented a stress-mediated rise in plasma norepinephrine concentration. The relation of ET-1, oxidative stress, and levels of epinephrine and norepinephrine concentrations, as well as the role of the sympathetic nervous system that would appear to be excluded, remain unclear, however, from the present study. Are ET\textsubscript{B} receptors mediating the pressor response or do ET\textsubscript{A} and ET\textsubscript{B} interact to participate in these findings, explaining the effect of the ET\textsubscript{A/B} receptor antagonist? Unfortunately, the authors did not test a pure ET\textsubscript{B} receptor antagonist that would have provided an answer to this question. What is the source of oxidative stress? Studies in the past have demonstrated that NADPH oxidase, xanthine oxidase, and mitochondria may be sources of superoxide in response to ET-1 stimulation. Inhibition of these different sources of reactive oxygen species is needed to test the origin of the superoxide mediating the stress effects in the current paradigm. Finally, because these responses are found in prehypertensive Dahl salt-sensitive rats, what do they tell us about what happens in either salt-sensitive or salt-resistant prehypertensive or hypertensive humans? We know from studies of mice that overexpression prepro–ET-1 restricted to the endothelium that large increases in the production of ET-1 may induce hypertrophic vascular remodeling and endothelial dysfunction, as well as upregulation of inflammatory mediators, but not hypertension, which probably requires complex interactions that include a positive sodium and fluid balance. Thus, the mechanisms demonstrated in the study by D’Angelo et al\textsuperscript{9} probably participate in acute BP elevations, but their role in the long-term elevation of BP of Dahl salt-sensitive rats or humans remains unclear. Further studies will be necessary to elucidate some of these questions, particularly using patient-oriented research approaches to translate these findings into therapeutic progress in human hypertension.
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