The article “Role of extracellular superoxide dismutase in the mouse angiotensin slow pressor response” describes studies in EC-SOD knockout and wild-type mice by Welch et al. This study is a continuation of a series of investigations by these researchers who have advanced our understanding of the role of reactive oxygen species (ROS) in the pathogenesis of hypertension. Of particular note, this group combines sophisticated physiological measurements (renal hemodynamics and conscious blood pressure [BP] by telemetry) with in vitro measures of protein and mRNA expression, as well as markers of oxidative stress.

There is clear evidence that increased oxidative stress is both a cause and a consequence of hypertension. Oxidative stress means that an imbalance develops between the pro-oxidant and antioxidant systems, with increased ROS generation and/or decreased antioxidant capacity. There are many oxidases responsible for ROS production and many antioxidant defenses, in both intracellular and extracellular locations. Dissecting the role of individual players is quite difficult, because, for example, there are 3 species of SOD, including EC-SOD, but no selective EC-SOD inhibitors are available. This study exploits the availability of the EC-SOD knockout mice to investigate the importance of this enzyme in BP control.

One novel observation in this study is the demonstration that young adult EC-SOD knockout mice exhibit an elevated baseline BP of ≈10 mm Hg, as well as an increase in renal vascular resistance and indices of increased oxidative stress. The BP measurements are made using the state-of-the-art technique, that is, telemetry, which allows detection of fairly subtle BP differences and eliminates stress-induced artifacts as seen with the tail-cuff method. This probably explains why a previous study using the tail-cuff method could not detect a BP difference between the knockout and wild-type mice. In older EC-SOD knockout mice where there was no detectable difference in BP measured by telemetry versus wild types, this may reflect an age-dependent loss of antioxidant capacity in the wild type.

The authors conclude that EC-SOD has a rather small role for in the physiological regulation of baseline BP, although from a clinical viewpoint, a ≈10-mm Hg elevation in mean BP is certainly significant. Also, developmental/adaptive changes in the knockout animal may mask the full importance of a specific protein. The main objective was to assess the importance of the EC-SOD in the slow pressor response to angiotensin II (Ang II). Chronic administration of low doses of Ang II, which do not evoke an immediate pressor response, nevertheless elicit a slowly developing hypertension over several days. The slow pressor response is seen in many species (rats, mice, rabbits, dogs, and swine) and in humans and is of potential clinical relevance, because many patients with essential or renovascular hypertension exhibit near normal Ang II levels but respond to converting enzyme inhibitors and angiotensin receptor antagonists with a fall in BP.

Both EC-SOD knockouts and the wild type showed a delayed rise in BP with the low-dose Ang II, although this was blunted in the EC-SOD knockouts, by ≈10 mm Hg compared with the wild type. It is perhaps surprising that the rise in BP is blunted in the EC-SOD knockout, because these mice clearly have endothelial dysfunction because of excess superoxide, and one might have predicted an enhanced pressor response to Ang II. However, this blunting of the response to Ang II is equal to the baseline rise in BP in the knockout, suggesting there may be a limit to the superoxide-induced rise in BP. The time course of the rise in BP during the slow pressor response, as well as the absolute value of the BP achieved after 5 days of Ang II, was similar between strains. The slow pressor response to Ang II is thought to be a ROS-dependent effect with activation of NADPH oxidase and, in the wild type, there is a delayed downregulation of EC-SOD. Any contribution made to the slow pressor response by EC-SOD is obviously absent in the EC-SOD knockout, hence the 10-mm Hg blunting of the Ang II response. Thus, the residual rise in BP seen in the knockout is a separate component to the slow pressor response, which is independent of the presence or absence of EC-SOD. What causes the EC-SOD-independent component of the slow pressor response, seen in the knockouts? The most likely explanation is that increased Ang II–dependent ROS exceed the buffering capacity of the other antioxidant systems, although neither markers of oxidative stress measured in the present study, isoprostane and malondialdehyde, were further elevated during the slow pressor response in the EC-SOD knockouts, arguing against Ang II–induced increases in oxidative stress in the knockout. However, these workers reported previously that tempol, a membrane-permeable SOD mimetic, was able to completely prevent the slow pressor response because of AngII in the wild-type mouse. Tempol provides a pharmacological method to preserve SOD activity,
consequently reducing oxidative stress and preserving NO. So, if an oxidative stress-independent component exists in slow pressor response, how can tempol completely prevent the slow pressor response in wild-type mice treated with low doses of Ang II? Tempol may have an oxidative stress-independent effect to reduce the slow pressor response. Alternatively, the EC-SOD-independent component of the slow pressor response may reflect the delayed direct action of Ang II and/or activation of other vasoconstrictor agents. For example, Ang II infusion increases thromboxane production, and the thromboxane receptor knockout mouse has a blunted slow pressor response to Ang II. Alternatively, the EC-SOD-independent component of the slow pressor response may reflect the delayed direct action of Ang II and/or activation of other vasoconstrictor agents. For example, Ang II infusion increases thromboxane production, and the thromboxane receptor knockout mouse has a blunted slow pressor response to Ang II. Also, endothelin blockade reduces the slow pressor response to Ang II infusion in the rat. It is also possible that the markers of oxidative stress used in this study (malondialdehyde and isoprostanes) are not reflective of the overall redox state and that other ROS are contributing to the slow pressor response in the EC-SOD knockout that are not detected by these measures. Despite these remaining uncertainties, the observations of Welch et al clearly show that in the total absence of EC-SOD there is a blunting in the slow pressor response to Ang II that is equivalent to the baseline rise in BP in the EC-SOD knockout.

The complexity of the interplay between the antioxidant defenses and the pro-oxidant systems and their impact on BP makes the interpretation of in vivo studies very complicated. Elegant physiological studies, such as the article by Welch et al in this issue, are necessary to unravel the relative importance of the different contributors to oxidative stress in the final control of the BP. An understanding of the precise causes of increased ROS in any given situation is essential for effective treatment of hypertension, because, as Vaziri points out, all oxidative stress is not equal, and antioxidant therapies need to be tailored to the specific source of the ROS.

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