Renal Blood Flow Autoregulation

What are the contributions for nitric oxide or superoxide to modulate the myogenic response?

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The maintenance of a constant renal blood flow and glomerular filtration rate in the face of physiological changes and pathological states is essential for proper fluid and electrolyte homeostasis. This phenomenon has been named renal autoregulation and comprises of two major mechanisms, the myogenic response and tubuloglomerular feedback. The myogenic response is not unique to the kidney and is a major contributor to maintain blood flow to organs in the face of changes in perfusion pressure. The vascular myogenic response was first described over a century ago and is an inherent vascular smooth muscle cell mechanism that is modulated by hormonal and paracrine factors (1, 16). Although the endothelium does not directly contribute to the myogenic response, endothelial-derived factors such as nitric oxide and epoxyeicosatrienoic acids can modulate the myogenic response (2, 7). The primary focus of experimental studies in the research paper published by Dr. Moss et al. was to define the effect of nitric oxide synthase (NOS) inhibition on dynamic characteristics of renal blood flow autoregulation in mice and focus analysis on the time and frequency domains (17). Provocative data provide initial evidence that NOS inhibition through potential actions on superoxide modulates the first stage of the myogenic response resulting in an enhanced myogenic renal blood flow autoregulatory response.

Numerous investigations have evaluated NOS, nitric oxide (NO), superoxide, and cGMP on renal blood flow autoregulation, the myogenic response, and tubuloglomerular feedback during steady-state conditions (5, 6, 9, 11, 12, 15). These studies have employed various experimental techniques, different species, pharmacological agents, and genetic animal models (3, 10). An overwhelming amount of published studies have concluded that endothelial-derived NO and NO metabolic pathways are not a critical component of the steady-state myogenic response or renal blood flow autoregulation (3, 18, 19). On the other hand, NO and NO metabolic pathways do modulate these responses with NO donors attenuating and NOS inhibition enhancing the myogenic response and renal blood flow autoregulation (5, 6, 11). Utilizing pharmacological agents the
findings Moss et al. confirm that NOS inhibition enhances the speed of the renal blood flow autoregulatory responses and using time and frequency domain analysis demonstrate that the effect is on the initial first stage of the myogenic response (17). Additional provocative data is presented that the enhanced myogenic response is dependent on superoxide (O$_2^-$) constrictor actions on the renal vascular smooth muscle.

Experiments described in this research report are technically very challenging and required the constant measurement of femoral artery blood pressure and renal blood flow in renal denervated mice. The expertise of this research team allowed for comprehensive analysis of renal blood flow autoregulation and time and frequency domains. A sophisticated aortic snare was employed to achieve changes in renal perfusion pressure. In all experimental settings the snare was used to lower renal perfusion pressure by 20 mmHg and then quickly released. Renal blood flow responses following release of the aortic snare were collected and analyzed. Analysis revealed two distinct stages from 0-5 seconds and 5-13 seconds with the second stage continued beyond a 100% response and ending at 19 seconds. In another set of experiments ureteral occlusion and 10% mannitol infusion were used to eliminate the tubuloglomerular feedback component. These experiments revealed that the first two stages were due to myogenic mechanisms. Analysis did reveal that the tubuloglomerular feedback response did contribute the overshoot of renal vascular resistance between 15 and 60 seconds. Overall, these findings are consistent with the majority of published studies that demonstrate that the myogenic response is the major contributor and early stage contributor to renal blood flow autoregulation and that the tubuloglomerular feedback acts as a late modulator and chronic regulator of renal blood flow autoregulation (3, 4, 8, 13, 14, 20, 21).

Next, the non-selective NOS inhibitor L-NAME was evaluated on renal blood flow autoregulation in mice. Mice treated with L-NAME had a greatly reduced renal blood flow and increased blood pressure. NOS inhibition changed the time and frequency domains with
autoregulatory efficiency in the time domain increasing in the first 2 seconds and a pronounced oscillatory response at a frequency of 0.25Hz. The oscillatory response originated in stage 1 and persisted through stage 2. The contribution of the superoxide pathway to the L-NAME response was evaluated by giving the SOD mimetic tempol following L-NAME. Tempol given in the presence of L-NAME normalized the initial rate for stage 1 and greatly attenuated the oscillations observed with NOS inhibition. Lastly, intravenous infusion of vasopressin (AVP) was utilized to determine the effect of increased blood pressure on the response to NOS inhibition. AVP reduced the duration of stage 1 but did not alter the frequency domain or stage 2 of the autoregulatory response. These data demonstrate that the effect of NOS inhibition is not related to increased blood pressure. Further analysis provides evidence that NOS inhibition enhanced the vascular smooth muscle cell myogenic response and did not inhibit the tubuloglomerular feedback signaling mechanism.

Taken as a whole, these experimental studies provide intriguing data on renal blood flow autoregulation and the effects of NOS inhibition on the time and frequency domains in early stages. These are technically challenging experiments that provide specific insight into the renal blood flow autoregulatory response. Because these experiments were not coupled to other types of experimental approaches the exact contributions for NO and superoxide remains ill defined. A pharmacological approach to employ NOS inhibition with subsequent addition of a SOD mimetic makes it difficult to define the roles of NO and superoxide. Other pharmacological approaches such as using NO donors would have addressed this issue from a different angle. The wide availability of genetically manipulated mice could have been combined with pharmacological manipulation of NOS and SOD. Moreover, other experimental approaches could have been utilized to provide insight concerning NOS and SOD to renal blood flow autoregulation. For example, increasing the magnitude and number of step changes in renal perfusion pressure and evaluating cortical and medullary blood flow would have provided interesting data to couple with the current findings.
Isolated renal microvessels would have allowed for a more definitive data on the interaction between NOS and SOD enzymes to the myogenic response. Last but not least, biochemical measurements and assessment of the NOS and superoxide pathways would have provided essential data supporting NO and superoxide as the key contributors. Although time-dependent biochemical analysis to determine the contribution for NOS and superoxide pathways to the dynamic characteristics of renal blood flow autoregulation will prove particularly challenging. It is unfortunate that supporting data using a couple of these approaches was not employed to further evaluate the complex interaction between NOS and SOD enzymes to modulate the myogenic response and renal blood flow autoregulatory time and frequency domains.

There is one set of data presented that really puts into question the conclusion that, “NOS inhibition leads to an exaggerated myogenic response as a result of attenuated NO production, less quenching of O$_2^-$, and the augmented actions of the vasoconstrictor O$_2^-$” (17). NOS inhibition increased blood pressure and decreased renal blood flow; however, adding tempol lowered blood pressure but did not increase renal blood flow. Thus, if SOD dismutase is eliminating the vasoconstrictor actions of O$_2^-$ then renal blood flow should have increased in the presence of tempol. Interestingly, AVP increased blood pressure but did not alter renal blood flow. Taken together, the effects of L-NAME, L-NAME and tempol, and AVP on renal blood flow and blood pressure provide more questions about NO and superoxide contributions to modulate the myogenic response than answers. Then again, it is clear from the experimental data presented that NO and superoxide participation in dynamic responses is more complex than steady-state conditions.

The experimental findings of Moss et al. provide thought-provoking data on the potential contribution for NO and superoxide to renal blood flow time and frequency domains for autoregulation and myogenic response modulation (17). A major finding of this study is that the myogenic response is responsible for the first 2 stages of renal blood flow autoregulation and can
efficiently regulate renal blood flow independent of tubuloglomerular feedback in response to a step change in renal perfusion pressure. NOS inhibition and SOD mimetic pharmacological manipulation presents initial data that metabolites of these enzymatic pathways interact in a complex way to modulate the renal blood flow autoregulatory myogenic response. Even though the myogenic response and renal blood flow autoregulation and the contribution of NO and superoxide pathways have been extensively studied during steady-state conditions (3, 9, 14, 18), the true contribution of NO and superoxide to modulate the myogenic response and renal blood flow autoregulation remains inconclusive. The findings of this current study using a technically challenging experimental approach provides the groundwork for future studies to better define the specific contributions for NO and superoxide to modulate the dynamic characteristics of the myogenic response and renal blood flow autoregulatory time and frequency domains.

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