The following is the abstract of the article discussed in the subsequent letter:

DiBona, Gerald F., and Linda L. Sawin. When the renal nerves are stimulated with sinusoidal stimuli over the frequency range 0.04–0.8 Hz, low (<0.4 Hz) but not high (>0.4 Hz)-frequency oscillations appear in renal blood flow (RBF) and are proposed to increase responsiveness of the renal vasculature to stimuli. This hypothesis was tested in anesthetized rats in which RBF responses to intrarenal injection of norepinephrine and angiotensin and to reductions in renal arterial pressure (RAP) were determined during conventional rectangular pulse and sinusoidal renal nerve stimulation. Conventional rectangular pulse renal nerve stimulation decreased RBF at 2 Hz but not at 0.2 or 1.0 Hz. Sinusoidal renal nerve stimulation elicited low-frequency oscillations (<0.4 Hz) in RBF only when the basal carrier signal frequency produced renal vasoconstriction, i.e., at 5 Hz but not at 1 Hz. Regardless of whether renal vasoconstriction occurred, neither conventional rectangular pulse nor sinusoidal renal nerve stimulation altered renal vasoconstrictor responses to norepinephrine and angiotensin. The RBF response to reduction in RAP was altered by both conventional rectangular pulse and sinusoidal renal nerve stimulation only when renal vasoconstriction occurred: the decrease in RBF during reduced RAP was greater. Sinusoidal renal nerve stimulation with a renal vasoconstrictor carrier frequency results in a decrease in RBF with superimposed low-frequency oscillations. However, these low-frequency RBF oscillations do not alter renal vascular responsiveness to vasoconstrictor stimuli.

Responsiveness of the Renal Vasculature: Relating Electrical Stimulation to Endogenous Nerve Activity Is Problematic

To the Editor: Slow oscillations between 0.1 and 0.4 Hz are present in many cardiovascular parameters such as arterial pressure, heart rate, sympathetic nerve activity (SNA) and renal blood flow (RBF). While recent reviews have addressed the origins of such slow oscillations (11), it remains to be determined whether these oscillations serve a functional purpose. With regard to slow oscillations present in renal sympathetic activity we have previously shown these to produce an oscillation in RBF (6). An important aspect of these oscillations is that they occur over a background of mean SNA but are clearly present at naturally occurring levels of SNA and RBF (9). Previously, we speculated that these slow oscillations might increase the responsiveness of the renal vasculature. That is, a system in which the input was constantly being modulated may produce higher gain or faster responses than a system under only a steady mean level of input. DiBona and Sawin (3) have sought to test this concept by stimulating the renal nerves with a base frequency (1 or 5 Hz) and overlaying a sinusoidal modulation at a secondary frequency (0.02–0.6 Hz). They found that when the base frequency was 1 Hz no mean change in RBF occurred and no oscillations in RBF could be produced at the modulating frequencies. At a higher base frequency of 5 Hz, which did reduce mean RBF, subsequent modulating frequencies produced oscillations in RBF. However, reductions in RBF after renal arterial norepinephrine and angiotensin II were unaffected by the sinusoidal stimulation pattern at either base frequency. They conclude that low-frequency RBF oscillations do not alter renal vascular responsiveness to vasoconstrictor stimuli. Thus their data provide evidence against our hypothesis, albeit using nonphysiological stimuli. They further suggest that the lack of RBF responsiveness to the 1-Hz stimulation supports their long-standing hypothesis (2) that the renal response to activation of the renal nerves is in three phases, with low levels not affecting RBF and glomerular filtration rate, but being capable of increasing both renin release and renal tubular sodium reabsorption. As we have previously pointed out, electrical stimulation cannot mimic the naturally occurring rhythmicity of SNA (10, 14). Such stimulation is very useful in allowing one to provide a precisely controlled level of input to the renal nerves (5), but one must remember that it will activate generally all axons in the nerve bundle whereas the naturally occurring signal is one of modulation of the number of recruited nerves and their frequency of firing (12). Thus the important concept is not the absolute frequency of the electrical stimuli but rather how this relates to the endogenous level of SNA. Unfortunately, DiBona and Sawin’s study (3) does not provide this information. Furthermore, a number of experimental observations support the contention that the renal vasculature is highly responsive to SNA during normal activities.

Chronic recordings of RBF in rabbits living in their home cages reveal that under quiet resting conditions increases in SNA produced decreases in RBF (1). In unrestrained rats in which behavioral patterns were monitored, RBF was highest when the rats were fully relaxed/asleep and was decreased during a range of events such as grooming or eating (4). Temporarily denervating the renal nerves by topical infusion of local anesthetic significantly increased resting RBF and decreased RBF responsiveness to daily activities, indicating a role for the renal nerves in regulating RBF at resting levels of SNA. Finally in conscious rabbits, stimuli such as noise stress, air-jet stress, and hypoxia, which increase SNA by only 10–30%, all produced reductions in RBF (13). A major limitation in using electrical stimulation, not alluded to by DiBona and Sawin (3), is the difficulty
in determining what each level of stimulation (1, 2, or 5 Hz, etc) relates to in terms of changes in endogenous SNA. Previously, we have compared the reduction in blood flow during low-level electrical stimulation at 1 Hz against that achieved during reflex activation of SNA using hypoxia. One-Hertz stimulation in anesthetized rabbits, which reduced cortical blood flow (and RBF) by 20% (7), equated with the same reduction in blood flow during 10% hypoxia, where SNA increased 76% (8). Thus, while we concede that the functional significance of slow oscillations of SNA remains unknown, we also contend that DiBona and Sawin’s (3) three-phase hypothesis for the neural control of renal function requires further evaluation, using reflexogenic rather than electrical stimulation of the renal nerves.

REFERENCES


Reply

To the Editor: With the use of electrical stimulation of the renal nerves, it has been repeatedly demonstrated that renal sympathetic nerve activity (RSNA) may be increased to a level that does not affect renal blood flow (RBF) or glomerular filtration rate (GFR) but increases both renin release and renal tubular sodium and water reabsorption resulting in antinatriuresis and antidiuresis (reviewed in Ref. 3).

Drs. Malpas, Guild, and Evans believe that using electrical stimulation of the renal nerves to produce an increase in RSNA may not faithfully reproduce the increase in RSNA that is seen with reflex maneuvers. Therefore, they believe that the above-mentioned concept for the neural control of renal function requires further evaluation “using reflexogenic rather than electrical stimulation of the renal nerves.” It is the purpose of this response to indicate that studies “using reflexogenic rather than electrical stimulation of the renal nerves” have been previously performed by us and others.

In dogs (1, 2, 4, 9–11), activation of the carotid baroreceptor or somatic afferent receptor reflexes was used to produce reflex increases in RSNA. In rats (5–8), air-jet stress was used to produce reflex increases in RSNA. In all of these instances, the reflex-induced increase in RSNA did not affect either RBF or GFR but resulted in increases in renin release and renal tubular sodium and water reabsorption (with antinatriuresis and antidiuresis), which could be prevented by renal denervation.

In summary, it is respectfully submitted that abundant evidence has been available from published studies “using reflexogenic rather than electrical stimulation of the renal nerves” for a considerable period of time. This evidence unequivocally and unambiguously demonstrates that reflex-induced increases in RSNA, while not altering either RBF or GFR, produce antinatriuresis and antidiuresis, which can be prevented by renal denervation. These observations are in full agreement with those derived from experiments using electrical stimulation of the renal nerves to increase RSNA.

REFERENCES


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