Mechanisms of renal blood flow autoregulation: dynamics and contributions

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Just A. Mechanisms of renal blood flow autoregulation: dynamics and contributions. Am J Physiol Regul Integr Comp Physiol 292: R1–R17, 2007. First published September 21, 2006; doi:10.1152/ajpregu.00332.2006.—Autoregulation of renal blood flow (RBF) is caused by the myogenic response (MR), tubuloglomerular feedback (TGF), and a third regulatory mechanism that is independent of TGF but slower than MR. The underlying cause of the third regulatory mechanism remains unclear; possibilities include ATP, ANG II, or a slow component of MR. Other mechanisms, which, however, exert their action through modulation of MR and TGF are pressure-dependent change of proximal tubular reabsorption, resetting of RBF and TGF, as well as modulating influences of ANG II and nitric oxide (NO). MR requires < 10 s for completion in the kidney and normally follows first-order kinetics without rate-sensitive components. TGF takes 30–60 s and shows spontaneous oscillations at 0.025–0.033 Hz. The third regulatory component requires 30–60 s; changes in proximal tubular reabsorption develop over 5 min and more slowly for up to 30 min, while RBF and TGF resetting stretch out over 20–60 min. Due to these kinetic differences, the relative contribution of the autoregulatory mechanisms determines the amount and spectrum of pressure fluctuations reaching glomerular and postglomerular capillaries and thereby potentially impinge on filtration, reabsorption, medullary perfusion, and hypertensive renal damage. Under resting conditions, MR contributes 50% to overall RBF autoregulation, TGF 35–50%, and the third mechanism < 15%. NO attenuates the strength, speed, and contribution of MR, whereas ANG II does not modify the balance of the autoregulatory mechanisms.

Autoregulation of blood flow describes the function of a vascular bed to maintain its perfusion constant despite variations of the level of arterial pressure. This function is present in almost any tissue but is particularly pronounced in some organs, such as brain and kidney. Autoregulation of renal blood flow (RBF) has long been recognized (153, 202). It has since been extensively studied and is well characterized under steady-state conditions as summarized in many excellent review articles (78, 87, 123, 139, 168, 199). It is thought today, that RBF autoregulation is based on two mechanisms, the myogenic response (MR) and the tubuloglomerular feedback (TGF). MR is a function of smooth muscle to contract in response to external stretching force. In the case of vascular smooth muscle, this causes vasoconstriction on a rise in arterial pressure, thus allowing for autoregulation. TGF is a more complicated mechanism specific to the kidney that leads to constriction of the afferent arteriole in response to an increase in sodium chloride concentration in the early distal tubule, the latter of which is a function of tubular flow rate.

However, much less is known about the relative contribution of MR and TGF and whether additional mechanisms are involved. This gap of knowledge is largely due to the difficulty in eliminating MR without also affecting TGF. Studies assessing these questions have generally relied on inhibition of TGF and the assumption that the remnant regulation is due to MR alone, which may leave additional mechanisms undetected. Another approach is based on the differences in the dynamics of MR and TGF (78). Such studies have helped in defining the characteristics of MR and TGF, detecting their contributions and interactions, and also providing evidence for a third regulatory mechanism.

The New Investigator Award in Regulatory and Integrative Physiology was established to encourage young investigators to continue research careers in cardiovascular, renal, and neuroendocrine integration. The award is presented annually at the Water and Electrolyte Homeostasis Section to a new investigator who has made important contributions to our understanding of the integrative aspects of cardiovascular, renal, and neuroendocrine physiology in health and disease.
Due to the difference in dynamics of MR, TGF, and a third regulatory mechanism, the balance of their contributions are an important determinant for the kinetics and function of the overall autoregulation. Since MR is faster than TGF and the third regulatory mechanism, the overall adaptation will become faster when the balance is shifted toward predominance of MR. The overall speed of RBF autoregulation is crucial, because the kidney vasculature is continuously challenged by fluctuations of pressure over a broad range of frequencies from cycle lengths of seconds and minutes (4, 49, 144, 146) to hours and days (20, 120, 126) (see Fig. 2A). Since autoregulation determines the amount of pressure fluctuations reaching the glomerulus, peritubular capillaries, and the medullary circulation, its function is potentially important for filtration, reabsorption, pressure natriuresis, and hypertensive renal damage.

The present article will briefly summarize the current knowledge about the mechanisms underlying RBF autoregulation, and will then describe in more detail their dynamic characteristics and relative contribution to the overall autoregulatory function.

**Autoregulatory Mechanisms**

It has been known for a long time, that the autoregulation of RBF is associated with that of glomerular filtration rate (GFR), indicating that it derives from adaptation of resistance in the preglomerular part of the vascular tree (58, 177, 179a). It is thought today that RBF autoregulation is caused by the combined action of both MR and TGF (139). More recent evidence indicates the participation of a third regulatory mechanism that is independent of TGF and slower than MR (96–98, 215). In addition, other mechanisms play an important role. However, since the latter mechanisms exert their function through modulation of MR and TGF, these may not constitute separate entities of regulatory mechanisms.

**MR.** The MR is a function of smooth muscle to contract in response to stretching force (91). In the case of vascular smooth muscle, a rise in intraluminal pressure induces a vasoconstriction, which not only overcomes the passive tension of the elastic vascular wall but, at least in small resistance vessels, reduces the diameter below the one at lower pressure. This causes an increased vascular resistance at higher pressure and allows for autoregulation of flow.

The signaling pathways underlying MR have been studied extensively and are reviewed in many excellent articles (39, 42, 44, 128, 135, 137, 156, 171). Therefore, only a brief overview shall be given here. One of the early events following myogenic activation is depolarization of the cell membrane. The stretch-dependent step preceding the depolarization, however, is still unclear. Possibilities include mechanosensitive ion channels, activation of integrin receptors, or stretch-induced activation of phospholipase C. Once initiated, the depolarization is thought to lead to influx of Ca^{2+}, mainly through voltage-gated Ca^{2+} channels. Release of Ca^{2+} from intracellular stores and increases in inositol 1,4,5-trisphosphate may accompany myogenic activation, but their importance for the final constrictor response of MR are unclear and seem marginal. The main signaling pathway following the rise in Ca^{2+} involves calmodulin and myosin light chain phosphorylation, although other pathways, such as cytochrome P-450, protein kinase C, rho-kinase, and myosin phosphorylase have also been implicated.

**TGF.** TGF is a regulating mechanism specific to the kidney that leads to vasoconstriction of the afferent arteriole in response to an increase in the luminal concentration of NaCl at the macula densa in the early distal tubule (111, 169). Because salt reabsorption from the ascending part of the loop of Henle is an active and more rate-limited process than the passive diffusion of water out of the descending loop, the concentration of NaCl reaching the macula densa is dependent on the rate of tubular flow with larger flow resulting in a higher distal tubular concentration. An increase in arterial pressure will enhance tubular flow due to enhanced glomerular filtration and reduced proximal tubular reabsorption. This will raise the NaCl concentration at the macula densa and cause afferent arteriolar vasoconstriction, providing restoration of filtration and autoregulation of RBF.

A large number of studies have provided substantial insight into the signaling pathways of the TGF as summarized in many comprehensive reviews (15, 19, 87, 88, 111, 139, 168, 169, 187). Only a brief synopsis will be given here. There is wide agreement that the initial absorption of NaCl through furosemide-sensitive Na^{+}-K^{+}-2Cl^{-} cotransport results in release of ATP from macula densa cells (15, 87, 111, 168), probably mediated through changes in intracellular concentrations of Na^{+}, Cl^{-}, and Ca^{2+}, depolarization, cell swelling, or alkalinization (15, 111). However, controversy exists regarding the further fate of the released ATP. One line of evidence supports the view that ATP directly activates ATP-specific purino receptors of the P2X1-type located on the afferent arteriole (87, 139, 140). Other results support the concept that ATP is converted to adenosine by nucleoside triphosphate diphosphohydrolase 1 (30) and 5'-nucleotidase (109) in the interstitial space of the juxtaglomerular apparatus, which then acts on A1-adenosine receptors of the P1-group of purino receptors (163, 168, 169).

A third regulatory mechanism. As described above, detection of additional regulating mechanisms has been complicated by the difficulty in eliminating MR without also affecting TGF. An alternative approach is to distinguish between mechanisms based on their differing kinetics. As explained in more detail below, MR is considerably faster than TGF. Accordingly, when challenged with a very rapid change in arterial pressure, the mechanisms respond in sequence corresponding to their intrinsic response times. An example of the response of RBF autoregulation to a quick rise in arterial pressure starting at time t = 0 s is shown for dogs, rats, and mice in Fig. 1. Under control conditions (red solid lines), resistance (RVR) quickly rises, but only during the initial 5–10 s. After a few seconds delay, i.e., at 6–10 s after the pressure step in rats and mice (Fig. 1, B and C) and at ~30 s in dogs (Fig. 1A), a secondary rise of RVR begins, sometimes reaching a slight overshoot at ~20 s in mice (Fig. 1C), 20–30 s in rats (Fig. 1B), and 40–50 s in dogs (Fig. 1A). Based on the response times explained in the next section, the primary rise in RVR is ascribed to MR and the secondary one to TGF. It can be seen in all three species, that another component is also involved, providing for an adaptation that is slower than 50 s taking about 2 min for completion. If only MR and TGF were contributing to the autoregulatory adaptation, then elimination of the slower TGF should leave only a singular rapid adaptation provided by MR.
Should an additional slower mechanism be involved, then the adaptation in the absence of TGF should consist of the fast MR followed by a slower mechanism. As can be seen in Fig. 1 (black broken lines), during TGF inhibition by furosemide MR is accompanied by a slower mechanism in all three species, indicating the presence of a third regulatory component. Although it cannot be excluded from these pharmacological experiments in dogs and rats (Fig. 1, A and B) that the slower adaptation is caused by incomplete inhibition of TGF, this seems unlikely from preliminary data shown in Fig. 1C. In these experiments, TGF was ablated genetically in mice deficient for the A1-adenosine (A1A) receptor (A1AR), which is known to be devoid of TGF (26, 185). These animals also show a slow component of autoregulation following the initial MR (Fig. 1C). However, for methodological reasons, TGF and its absence in A1AR-deficient animals has been measured only in superficial cortical nephrons (26, 185). The possibility exists, therefore, that other nephrons might differ in the signaling pathways of TGF so that some of them might maintain a functional TGF even in the absence of A1ARs. However, if TGF should remain functional in a major fraction of nephrons in the absence of adenosine signaling, then additional global TGF inhibition by furosemide should further reduce autoregulatory efficiency in these animals. This is clearly not the case (Fig. 1C).

Other investigators, using a mathematical deconvolution technique, also found evidence for a slow third regulatory component that is resistant to TGF inhibition with furosemide (215). A slow autoregulatory mechanism has also been observed in response to step changes in arterial pressure in a hypotensive pressure range (65–75 mmHg) (36). However, analysis of autoregulatory responses to step changes in perfusion pressure measured in juxtamedullary afferent arterioles, where TGF is dominant, showed that the faster response was resistant to inhibition of TGF by furosemide does not further reduce autoregulation, indicating that TGF is independent of TGF but slower than MR. Note that during furosemide, MR becomes stronger, indicating interactions between TGF and MR rather than simple additive contribution. Genetic inhibition of TGF by targeted deletion in A1AR mice reduced total autoregulatory efficiency by a similar amount as furosemide. This confirms genetically the contribution of TGF to autoregulation. Autoregulation continues to include a slow autoregulatory component in A1AR mice, demonstrating the presence of a slow TGF-independent autoregulatory mechanism. Additional pharmacological inhibition of TGF by furosemide does not further reduce autoregulation, indicating that A1AR mice do not maintain a remnant TGF activity.
to the relevant receptors in the juxtaglomerular apparatus to completely block renal interstitial production of ANG II. Further studies, including ANG II (AT1A and B) receptor-deficient animals are required to clarify the role of ANG II. With regard to the controversy about ATP or adenosine-mediating TGF, an attractive hypothesis is that ATP acting on P2X1 receptors might not mediate TGF but instead be the underlying cause of the third regulatory mechanism. This would also help in solving the controversy concerning the mediator of TGF. This hypothesis, however, awaits experimental testing. Another possibility is that the slow TGF-independent regulation reflects a slow component of MR. However, as discussed in more detail below, observations of MR in isolated vessels do not typically support the presence of a biphasic time course for MR (35, 43, 91); even in those cases in which an initial rate-sensitive component of MR was described, the latter only gave rise to an initial overshoot but not a secondary slow component (60, 90). Furthermore, direct comparison of autoregulatory responses between the hindlimb and kidney revealed only a monophasic adaptation in skeletal muscle with virtually identical dynamics as those ascribed to MR in the kidney but no indication for a slower component (97).

Other regulating mechanisms. Although the following mechanisms likely play important roles for overall renal function, they may impair rather than support a strict constancy of RBF and/or they may impact RBF autoregulation through modulation of MR or TGF and may thus not constitute separate entities. The first category includes “resetting” of total RBF and of TGF. The second category comprises the multitude of paracrine and hormonal factors modulating the strength of MR and TGF, which shall only briefly be mentioned here (see Ref. 139 for a review). Other members of the second category are pressure-dependent modulation of proximal tubular reabsorption (127) and possible regulating influences of NO (100, 196, 197).

Resetting of RBF. Prolonged reduction of RBF for 20–30 min leads to a reduction of the baseline level of RBF on which autoregulation is operating (36, 55, 74, 136, 180–182). This resetting of the set point of autoregulation seems to be mediated predominantly by pressure-dependent stimulation of the renin angiotensin system as it is abolished by ACE-inhibition (36, 74, 136, 182), ANG II receptor antagonism (36), and clamping of ANG II levels (182). The underlying mechanism is probably ANG II-induced modulation of afferent and efferent arteriolar resistances (180). A similar shift of the autoregulated baseline level of RBF can also be induced experimentally by infusion of ANG II (71, 106). Conversely, ACE-inhibition (7, 69, 138, 145) or ANG II receptor antagonism (1, 5, 7, 69, 145) elevates the set point of RBF, suggesting that this mechanism might partly be activated during resting conditions. It should be kept in mind, however, that resetting of the RBF set point in downward direction during reduction of arterial pressure, i.e., into the direction of the initial perturbation, implies an impairment of the capability of keeping RBF constant. However, this effect appears to be predominantly activated during prolonged and hypotensive reductions rather than elevations of arterial pressure. The relevance for everyday physiology, therefore, remains open.

Resetting of TGF. Prolonged activation of TGF by an enhanced tubular fluid load leads to resetting of the TGF function curve by shifting the set point of TGF toward higher tubular flow rates (48, 189, 190; reviewed in Refs. 19 and 191). As for RBF resetting, such resetting of TGF implies that it losses its regulatory strength to correct the perturbation over a prolonged period of time. The advantage is that TGF retains its regulatory strength to buffer shorter-term fluctuations around this new set point (19, 191). The resetting of TGF is mediated by NO produced from the neuronal isoform of NOS (nNOS), which is located in the macula densa, whereas ANG II does not seem to be involved (19, 48). It shall be mentioned, however, that in response to more integrated stimulation, such as volume expansion, the modulation of the TGF function curve is more complex, and in addition to a shift of the set point, also includes a reduction of the overall magnitude and an upward shift of the function curve toward higher GFR (6, 21, 27, 149, 166, 188, 201). Under these conditions, ANG II also seems to be involved in the resetting (166), in addition to the role of nNOS (27). A similar type of TGF resetting, but in opposite direction (shift of the set point to smaller tubular flow rates and smaller magnitude), seems to occur during prolonged reduction of perfusion pressure (175).

Pressure-dependent modulation of proximal tubular reabsorption. An acute rise in renal arterial pressure not only increases single nephron GFR but also induces a progressive reduction of proximal tubular reabsorption (34, 67, 107, 204). The increase of fluid remaining in the distal tubule will add to the tubular load entering the loop of Henle and thereby enhance the error signal reaching the macula densa. Accordingly, a progressive reduction of reabsorption will slowly augment the regulatory strength of TGF (132). Although the pressure-dependent modulation of proximal tubular reabsorption may stretch out over a course of 20–30 min after the change in pressure, the majority of this adaptation seems to occur within the initial 5 min (34, 204, 222). Furthermore, the change in reabsorption has been found to be associated with a redistribution of Na\(^{+}\)-H\(^{+}\)-transporter (NHE3). Na\(^{+}\)-phosphate-co-transporter (NaPi2) in the proximal tubular epithelium from the tip of the apical brush border to the base of the villi and finally to intracellular vesicles, and accompanied by a reduction in Na\(^{+}\)-K\(^{+}\)-ATPase activity (124, 127, 222). The initial transporter redistribution from the tip to the base of the brush border in response to an increase of arterial pressure seems to be completed within < 5 min (124, 222), although the final redistribution to intracellular vesicles and the response in opposite direction in response to restoration of pressure back to the resting level may be slower, taking up to 20 min even after only 5 min of hypertension (222). Taken together, this secondary enhancement of TGF could provide for a slow RVR adaptation over a course of ~5 min. This mechanism might thus contribute to the slow rise in RVR seen beyond the initial 40 s during control conditions when TGF is fully functional, with a time course of 2 min or even more for completion (Fig. 1). In any case, however, this mechanism should be regarded as a slow component of TGF and clearly distinguished from the third mechanism of RBF autoregulation described above that seems to be independent of TGF.

Whether the slow component of autoregulation seen during control conditions [with a time course of 2 min or more for completion (Fig. 1)] is indeed caused by a slow component of TGF (with a time course of 5 min or more) or by the TGF-independent third mechanism (with an apparent time course
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Invited Review

The typical time course of the response of single arterioles to a rapid rise in intraluminal pressure consists of an initial passive distension followed by an active constric-
of 21 s observed in dogs (115), at least when considering that dogs have longer tubular loops than rats. The signal transduction from the macula densa to the afferent arteriole in response to changes in tubular NaCl concentration shows a delay of 3 s followed by a rapid vasoconstriction over another < 3 s so that the entire response is completed within 5–6 s (29). Taken together, the overall TGF response includes a lag time of 15 s, 11 s of which are due to tubular delays, and 3 s to signal transmission across the juxtaglomerular apparatus. The constrictor response itself seems to be fast (< 6 s), resembling the kinetics of MR in the kidney. The more sluggish overall response of TGF accordingly seems to be due to tubular effects.

In the intact animal, TGF shows spontaneous oscillations at a center frequency of 0.033 Hz or at a cycle length of 30 s (117). The same oscillations are also apparent in RBF by transfer function analysis between arterial pressure and RBF in anesthetized (38, 41, 81) and conscious rats (18, 116, 147). Similar oscillations of RBF are seen in conscious dogs, albeit at a lower center frequency of 0.025 Hz (Fig. 2B) (102, 161, 213), presumably due in part to longer loops of Henle. However, the oscillations are neither completely synchronized nor purely sinusoid, as the frequency may vary from nephron to nephron (76, 217), as well as over time in the same nephron (53, 223), including chaotic behavior that seems to be more irregular in genetically hypertensive animals (75).

Fig. 2. Transfer function analysis between spontaneous fluctuations of RAP and renal blood flow (RBF) in conscious resting dogs. A: spectral density of RAP fluctuations. Standard frequency ranges for high-frequency (HF) and low-frequency (LF) ranges in humans are indicated by horizontal bars. B: transfer function gain between RAP and RBF in decibels. Broken lines denote slopes of 20 and 40 decibels per decade (dB/dec) of frequency for comparison. C: phase delay between RAP and RBF in fractions of π. Data during control conditions (thick line, filled circles, n = 20) and during TGF-inhibition by furosemide (thin line, open circles, 1.3 mg/kg, n = 7). Data are consolidated from Refs. 99, 100, 102 with permission (means ± SE). Transfer function gain values > 0 dB denote absent, gain values < 0 dB efficient regulation. RBF autoregulation starts to become efficient for fluctuations slower than 0.1 Hz due to the action of MR. Between 0.01 and 0.1 Hz, a peak of higher gain centered at 0.025 Hz reflects feedback oscillations of TGF. Below 0.01 Hz, maximum regulatory efficiency is reached due to the action of both MR and TGF. Inhibition of TGF eliminates the gain maximum at 0.025 Hz, indicating that the loss of TGF improves autoregulation in this frequency range. Note that this is the case only at this limited frequency range of feedback oscillations of TGF. In contrast, the autoregulatory influence of TGF can only affect lower frequencies. A smaller gain maximum may appear at 0.016 Hz during furosemide, consistent with feedback oscillations of a third regulatory mechanism with a response time of 60 s. Phase delay does not exceed π/4 and the slope of gain reduction below 0.1 Hz does not exceed 20 dB/dec, both of which are characteristics of a first-order linear control system, which does not allow for a rate-sensitive component.

As noted above, prolonged stimulation of TGF leads to resetting of its set point, which will compromise its ability to buffer slow fluctuations of pressure. This confines the efficiency of TGF to a certain frequency window. The upper limit of this frequency range is determined by its response time, i.e., slower than its natural frequency of 0.033–0.025 Hz. The lower limit is a function of the development of resetting. Considering a resetting time of 20–60 min (189, 190), this suggests a lower frequency limit of 1/20 to 1/60 min or 0.001 to 0.0003 Hz.

Dynamics of other regulatory mechanisms. Resetting of RBF autoregulation during prolonged reduction of arterial pressure occurs over a time frame of about 20 min (36, 74, 182), implying a lower frequency limit of 0.001 Hz. It should be kept in mind, however, that this type of resetting seems to occur predominantly during chronic reductions, rather than elevations of arterial pressure, and only those to hypotensive levels, so that this frequency limitation might not be of major
importance in the normal animal. The augmentation of TGF by progressive reduction of proximal tubular reabsorption during a continued rise in arterial pressure develops over a period of 5–8 min and more slowly over up to 30 min (34, 204). This mechanism could thus contribute to the slow component of RVR adaptation beyond the initial 30 s in rats and mice and beyond 60 s in dogs. The slow component of this enforcement of TGF could partly offset the weakening effect induced by TGF resetting. The phasic modulatory role of fluctuations of NO detected in transfer function experiments has been observed in a frequency range of 0.001 and 0.01 Hz (2–20 min cycle length) (100). The counterregulatory influence of NO described by Ichihara and Navar (83) would be expected in a frequency range of 0.03 to 0.01 Hz (2–5 min) cycle length.

**Dynamics of overall RBF autoregulation.** Several approaches have been used to characterize the dynamic characteristics of the overall autoregulatory function.

**Step-response analysis.** The most simple method is the analysis of the time course of the response to a rapid step change in arterial pressure. The particular biphasic time course found in the kidney was probably first described by Thurau (195) and Waugh (208). It is known today that the early component of this biphasic response reflects MR, whereas the secondary component is mediated by TGF. Evidence for this concept was provided by Young and Marsh (220) by demonstrating that in response to a rapid step increase in arterial pressure the early response was already completed before distal tubular pressure, and thus any potential TGF signal, had even begun to rise. The response of RBF to an increase in arterial pressures was later investigated in more detail in dogs (98, 99), rats (36, 96, 97, 101, 122, 203, 215), and mice (101) as depicted in Fig. 1.

As described in earlier sections of this article, the typical response of RBF to a rapid increase in arterial pressure consists of an immediate reduction in RVR, followed by a rise that occurs in a biphasic manner with a primary increase within the first 10 s and a secondary one between 10 and 30 s in rats and mice, and between 30 and 50 s in dogs. The primary constriction response is most likely due to the action of MR as suggested by the similarity to the time course of MR in the kidney. The secondary response is thought to reflect TGF, since it corresponds to the time course of TGF and distal tubular pressure (220) and because it is reduced during impairment of TGF induced by furosemide (96–98, 101, 215, 215) (Fig. 1, A and B), genetic deficiency of A1 adenosine receptors (101) (Fig. 1C), interruption of tubular flow (203), or in the hydronephrotic kidney (122).

The initial reduction of RVR has been described by many authors (96, 101, 195, 208, 220) and is most likely due to passive distension of the resistance vessels as demonstrated directly in diameter responses of afferent arterioles (122, 203) and as typically seen in studies of MR in isolated arterioles (43, 91). The passive nature of this initial drop of RVR is demonstrated by its persistence and prolongation during smooth muscle paralysis with Ca\(^{2+}\)-channel blockade (96). This indicates that autoregulation of RBF not only has to reduce the diameter of the resistance vessels but also to overcome the passive elastic distension to achieve autoregulation. The active response of autoregulation therefore includes the change of RVR from the initial minimum to the final new steady state (Fig. 1).

A related method for investigation of the dynamics of autoregulation is to challenge it with ramp-shaped changes of renal artery pressure at different speeds. The influence of the autoregulatory mechanisms is reflected by the degree of hysteresis and reactive hyperemia during different ramp speeds (55, 56).

**Transfer function analysis.** Another approach is to analyze the transfer function between fluctuations of arterial pressure and RBF. This provides an autoregulatory index spread out over a range of frequencies. The resulting “gain” of the transfer function is similar to the ratio of the amplitude of normalized fluctuations of flow divided by those of pressure. In a rigid tube without autoregulation or compliance, flow changes by the same percentage as pressure and thus the gain will be 1 (or 0) decibel. In the presence of autoregulation, fluctuations of RBF are attenuated vs. those of pressure causing the gain to be smaller than 1 (negative decibel values). Conversely, gain values above 1 (> 0 dB) indicate that fluctuations in flow exceed those in pressure. This can result from resonance, capacitative filling of compliance vessels, or passive distension of resistance vessels.

A typical result of the transfer function derived from the natural fluctuations of pressure and RBF in conscious resting dogs is shown in Fig. 2B. At high frequencies, the transfer function displays a high gain, indicating absence of autoregulation. This is expected, since the fluctuations at this end of the spectrum are too fast for the autoregulatory response (Fig. 2B). When moving along the x-axis to the left toward slower frequencies, a point is reached where the gain becomes smaller, reflecting improving autoregulatory efficiency. The frequency at which the decline of the gain begins is denoted as “corner frequency.” In conscious dogs, this is found at ~0.1 Hz (Fig. 2B). Between 0.1 and 0.01 Hz, the decline of gain values is interrupted by a frequency range of higher gain centered at 0.025 Hz. This indicates enhanced fluctuations of RBF compatible with feedback oscillations. When moving further toward slower frequencies the gain continues to fall, indicating further improvement of autoregulation until it levels off below 0.01 Hz.

Very similar results are found by many authors in conscious rats (18, 62, 116, 122, 147), anesthetized rats (2, 3, 38, 41, 79, 81, 179, 205–207), and conscious dogs (126, 161, 213). Results are also the same whether calculated from spontaneous fluctuations of pressure (2, 3, 9, 18, 62, 116, 122, 147, 161, 205, 207), from experimentally enhanced variations (41), or from forced oscillations (37, 79, 81, 179, 205, 206, 213). Other studies reported comparable results for parts of the spectrum, although their frequency range was either too high to include TGF (126, 159), too low to embrace MR (213), or lower than both mechanisms (126).

The corner frequency is thought to reflect the action of MR. Support for this view comes from comparison of this frequency (0.1–0.3 Hz, i.e., cycle length of 3–10 s) to the response time of MR in the renal circulation (3–10 s, see above), as well as to the transfer function of MR of intestinal smooth muscle (11). Further support is the observation that the corner frequency is not affected by inhibition of TGF during furosemide (3, 102, 179), ureter obstruction (41), or in the hydronephrotic kidney (37). The peak of higher gain at 0.025 or 0.033 Hz is thought to reflect an action of TGF, because it corresponds exactly to the frequency of spontaneous feedback oscillations of TGF.
and relative contribution of MR to overall autoregulation. During control conditions, MR contributes 50% to the active autoregulatory response ANG II and does not affect this contribution. In contrast, NOS-inhibition profoundly elevates speed, strength, and relative contribution of MR to overall autoregulation.

(80, 117) and is absent during TGF-inhibition (3, 41, 102, 179) (Fig. 3), as well as in the hydropnephrotic kidney (37). It may seem counterintuitive that elimination of a regulating system, such as TGF, leads to a reduction of the gain of the transfer function, i.e., improving autoregulation. It should be appreciated, however, that the gain peak at ~0.03 Hz reflects feedback oscillations of TGF at its resonance frequency but not its regulatory influence. Any control system showing feedback oscillations, such as TGF, is incapable of contributing to autoregulation at the resonance frequency, but can do so only for fluctuations occurring slower than this. Instead, at the resonance frequency, the feedback oscillations would rather add fluctuations and thus counteract autoregulation in this frequency range. The observation that in this frequency range TGF is counterproductive to autoregulation may raise the question of whether the purpose of TGF is not only the autoregulation of RBF but may also or primarily serve other functions, such as the regulation of water and electrolyte homeostasis (132).

The phase relation between pressure and flow shows two regions of larger phase at frequencies closely related to the frequency ranges of MR (corner frequency) and TGF (gain peak between 0.01 and 0.1 Hz) (2, 3, 11, 38, 41, 81, 102, 116, 179, 207). As expected, inhibition of TGF eliminates the TGF-related phase (0.01–0.04 Hz), but does not affect the MR-related phase (0.04–0.1 Hz) (3, 41, 102, 179).

Characteristics of the gain and phase spectrum also allow conclusions about dynamic features of the underlying regulatory system. In a first-order linear control system, gain will decrease below the corner frequency at a rate of 20 dB per decade of frequencies, while a second-order system without damping will show a slope of 40 decibels per decade (dB/dec). Furthermore, a first-order system will produce a delay of $\pi/4$ at its corner frequency, whereas a second-order control system, necessary to allow for a rate-sensitive component, can produce a phase shift of up to $\pi/2$ (57, 130). In this respect, it is noteworthy that the slope of gain reduction below 0.1 Hz typically resembles 20 rather than 40 dB/dec (Fig. 2B) (102, 147, 179, 207) and the phase reaches a value of $\pi/4$ rather than $\pi/2$ (Fig. 2C) (2, 3, 11, 38, 41, 81, 102, 116, 179, 207). These findings indicate that MR in the normal kidney operates as a first-order control system (or as a dampened second-order system), and thus does not seem to include a prominent rate-sensitive component. These characteristics are not fixed but may change. A higher phase closer to $\pi/2$ and a steeper slope of gain reduction closer to 40 dB/dec (179, 207) have been observed after NOS-inhibition, indicating that NO might be one of the factors providing dampening of second-order and thus rate-sensitive characteristics.

It is noteworthy that the gain for slow fluctuations below 0.01 Hz, which should correspond to steady-state autoregulation, is only ~5 to ~10 dB, indicating only 60–70% autoregulatory efficiency (Fig. 2B) as found invariably in all transfer function studies. This level of autoregulation is considerably less than the almost perfect autoregulation of >90% (i.e., more negative than ~20 dB), typically found by direct measurements of steady-state autoregulation (18, 102, 139). Initially this was interpreted as indicating that only part of the autoregulatory capacity is used under physiological conditions (102, 147). However, another possibility is that the transfer gain at these frequencies is not a reliable measure of autoregulatory efficiency. Although the transfer function correctly detects complete absence of autoregulation (102), more recent findings cast doubts that the method can distinguish between different degrees of partial and perfect autoregulation (18). In these experiments, rats with experimentally impaired autoregulation displayed unaltered transfer gain despite reduced steady-state autoregulation, as well as autoregulation-related glomerulosclerosis (18).

In the frequency range above the corner frequency (>0.1–0.3 Hz), the transfer function gain is high and autoregulation absent, because pressure fluctuations at these frequencies exceed the speed of the autoregulatory mechanisms. However, gain in this part of the spectrum is not at 0 dB as would be...
expected for a nonresponsive vascular system, but at a higher level (Fig. 2B), a phenomenon observed invariably by all authors. As mentioned above, this could derive from feedback oscillations, capacitance, or passive distension of resistance vessels. The persistence during Ca²⁺-channel inhibition (96, 102) speaks against active feedback oscillations as an underlying cause. The rather uniform distribution over all frequencies above 0.1 Hz favors passive distension over capacitance. However, some regions of higher gain above the corner frequency are occasionally observed (Fig. 2B) (41, 96, 102, 206), suggesting an additional role of capacitance.

Despite the passive nature of the renal vascular bed for fluctuations above the corner frequency of MR, it has been proposed that the kidney may nevertheless respond to faster frequencies particularly to those of pulse pressure at the frequency of the heart rate (122, 123). Due to a slightly longer delay time for the vasorelaxation response to the diastolic pressure decay than for the constrictor response to the systolic pressure rise, the repeated constrictor responses will accumulate more avidly than the vasodilator ones and produce an overall vascular tone above that induced by mean pressure alone. Although earlier studies did not detect a major influence of pulse pressure on RBF autoregulation (155, 176) and more recent measurements of RBF responses in intact rats suggested a considerably smaller, but still significant, difference in delay times (97), this interesting hypothesis of indirect response to pulse pressure fluctuations deserves further investigation.

**Summary of the dynamics of RBF autoregulation.** Taken together, the current knowledge indicates that overall autoregulation of RBF becomes effective below its upper frequency limit of 0.1–0.3 Hz (Fig. 2B) due to the action of MR, the latter of which shows a response time of < 5–10 s in the kidney (Fig. 1). For slower fluctuations, MR is joined by TGF, so that the complete dynamic response of MR and TGF is reached for frequencies slower than 0.01 Hz (Fig. 2). This corresponds well to the time of 60–120 s that is required for completion of the autoregulatory response to a step change in arterial pressure (Fig. 1). Between 0.01 and 0.1 Hz TGF is counterproductive to autoregulation in a confined frequency range due to its feedback oscillations around 0.025 Hz in dogs and 0.033 Hz in rats.

Note that the upper frequency limit of RBF autoregulation (0.1–0.3 Hz) is slower than the short-term variability of arterial pressure in the respiration-related HF-range (0.2–0.5 Hz in dogs and humans, 0.6–2.0 Hz in rats) and that autoregulation only starts to become effective in the sympathetically affected LF-range (0.04–0.15 Hz in humans 0.2–0.6 Hz in rats) (see Fig. 2A) (28, 94). Nevertheless, the majority of spectral power is located at lower frequencies at which RBF autoregulation is effective. Whether RBF may also respond indirectly to frequencies exceeding its direct regulation, such as pulse pressure, awaits further investigation.

As discussed above, RBF autoregulation may also be bound by a lower frequency limit, depending on the time course and influence of resetting mechanisms on TGF and autoregulation. From the time frame of 20–60 min for both types of resetting, the lower limit would be expected in a range of 0.0003 to 0.001 Hz. It should be recalled, however, that the resetting of total RBF autoregulation might not be of major influence at resting arterial pressure. The frequency limitation imposed by TGF-resetting might be partly compensated for by progressive augmentation of the error signal provided to the macula densa due to pressure-dependent reduction of proximal tubular reabsorption, although the bulk of the latter adaptation seems to occur faster than TGF-resetting.

**Contribution of the Autoregulatory Mechanisms**

**Contributions in the normal animal.** While it is now widely accepted that RBF autoregulation is due to both TGF and MR, and new evidence indicates an additional third mechanism, little is known about the balance of their relative contributions. Because of the different response times, the balance among the mechanisms determines the kinetics of the overall response and thus the frequency characteristics of the autoregulatory shield. The first quantification of the contributions of TGF and MR was achieved by micropuncture experiments measuring the degree of autoregulation in superficial cortical nephrons during acute or chronic inhibition of TGF (134). These investigations indicated a contribution of TGF of 30–60%. More detailed later studies using similar methods determined the participation of TGF more exactly to 50% (132, 167). A similar level of TGF participation (60%) was found in juxtamedullary nephrons (133, 186). The same conclusion was drawn from model calculations based on the separate autoregulatory strengths of TGF and MR (10, 132).

A limitation of the above investigations is that while the contribution of TGF is determined directly, the participation of MR is estimated from the assumption that autoregulation in the absence of TGF is exclusively due to MR. As discussed above, growing evidence indicates participation of a third regulatory mechanism. In addition, interactions exist between TGF and MR (133, 164), giving rise to the caveat that the strength of MR in the absence of TGF may not be the same as in the intact animal. These limitations can be avoided if the contribution of MR is determined directly even in the presence of TGF. This can be achieved by analyzing the time course of autoregulation during a rapid change in arterial pressure (96–99, 203, 215). Because MR is faster than the other mechanisms, its contribution is reflected by the autoregulation within the first 5–10 s (Fig. 1). To estimate the contribution to total autoregulation, it should be recalled that the initial reduction of RVR is a passive phenomenon of vessel distension (see above), so that total autoregulation includes the complete adaptation from the lowest RVR to the steady-state value. Investigations of this type indicate that MR contributes 30% between 100 and 145 mmHg in the isolated kidney (203), 35–45% between 50 and 95 mmHg in the conscious dog (Fig. 1A) (98, 99), and 50–55% during small pressure perturbations close to the physiological level from 90 to 110 mmHg in anesthetized rats (Fig. 1B) (96, 97) and mice (Fig. 1C) (101). Wronski et al. (215), using a mathematical deconvolution technique, indicate a much larger contribution of MR of 75–80%. Their data, however, was based on the regulatory response to a pressure step from complete arterial occlusion to 106 mmHg.

The contribution of the third regulatory mechanism is estimated from the slow autoregulation seen in the absence of TGF extending beyond the first 10 s (Fig. 1). The participation of this mechanism seems to be < 12% at the resting arterial pressure in rats (96, 97) (Fig. 1B), although it may provide up to 30% at lower arterial pressures between 50 and 110 mmHg in rats (Fig. 1B) (96) and dogs (Fig. 1A) (98). Depending on whether this mechanism is contributing when TGF is active
and considering a contribution of MR of 55%, the contribution of TGF is estimated as 45% (third mechanism not contributing when TGF is active, i.e., TGF = 100% - 55% - 0%) to 35% (third mechanism contributing 12% whether TGF is active or absent, TGF = 100% - 55% - 12%). Walker et al. (203) did not detect a third regulatory component in juxta- medullary afferent arterioles and estimated the contribution of TGF as 60%. Wronski et al. (215) reported a slow, third mechanism present in the intact animal with active TGF. The contribution of this mechanism, however, was < 10%. Although it seems likely from the time course, it is not proven yet whether the latter component reflects the third mechanism or TGF-dependent mechanisms or both. The final determination of the participation of the third regulatory mechanism in the normal animal with functional TGF has to await the clarification of its underlying cause so that it can be inhibited selectively.

Taken together, MR and TGF contribute ~50% each to the overall autoregulation of RBF. The third mechanism may contribute up to 12% in the absence of TGF. How much and whether it participates in the normal animal remains open at this time.

**Interactions between TGF and MR.** The balance of the mechanisms contributing to RBF autoregulation is not only determined by the algebraic summation of their influences, but also by interactions between them. The first and most direct demonstration of interactions between TGF and MR was provided by Schnermann and Briggs (164) who measured the efficiency of MR-mediated autoregulation when TGF was eliminated by holding tubular perfusion rate constant. Autoregulation was most efficient when TGF was held at a maximally activated state during high tubular perfusion and less efficient or absent at intermediate or halted perfusion. These results indicate a positive interaction, so that activation of TGF does not only induce vasoconstriction on its own but also promotes the autoregulatory vasoconstrictor response of MR. Other indications for interactions derive from the observation that inhibition of TGF not only reduces autoregulation in the segment immediately affected by TGF but also that in more upstream parts of the vascular tree (133). Furthermore, spectral analysis of the oscillations in single nephron blood flow demonstrated that the strength of MR-associated fluctuations varies with inhibition or activation of TGF (218). Similarly, analysis of the pattern of whole kidney RBF indicated nonlinear interactions between the two principal oscillations ascribed to MR and TGF (32, 33, 152). Communication of TGF responses to upstream vascular segments are also indicated by the fact that activation of TGF in one nephron causes a similar reaction in a neighboring nephron (103) and by the observation that synchronization of TGF-mediated oscillations occurs between nephrons deriving from the same interlobular artery but not between nephrons supplied by different parent vessels (77, 217).

The underlying cause of the interaction is not clear. Potential explanations are a physical coupling between myogenically active vascular segments through intravascular pressure changes (ascending MR) and cell-to-cell communication of vascular responses from the smooth muscle of the afferent arteriole to those of upstream segments (conducted vasomotor responses). These explanations are not mutually exclusive and probably coexist. The concept of the ascending MR was proposed and analyzed by several authors (52, 68, 91, 133).

Local intravascular pressures are distributed over the vascular tree in the same relative amount as the segmental resistances. A localized vasoconstriction in a certain segment of the vasculature will augment its contribution to the overall resistance and therefore to the overall pressure decay along the vascular tree. Accordingly, this will not only reduce intravascular pressure downstream of the vasoconstrictor site, but also raise the pressure in upstream segments. This rise will elicit MR in the latter segments and thereby extend the initial response in ascending direction. The other option, conduction of vasomotor responses, has been studied intensively in several vascular beds both for vasoconstrictor and for vasodilator responses (45, 54, 65, 172, 173). The signal is communicated via gap junction coupling either along the vascular smooth muscle cells or along the endothelial layer, or both. The strength of conduction as well as the preferred smooth muscle or endothelial pathway vary between vasodilator and vasoconstrictor responses (174), specific agonists (47), and possibly, also between vascular beds. Among the various connexins (Cx), i.e., the subunits forming the gap junctions, the predominant ones occurring in the vascular system are Cx37, Cx40, and Cx43 (66, 121). The same connexins are also present in the renal vasculature (8, 221), and conducted responses of intracellular Ca²⁺-concentrations in response to local electrical stimulation have been demonstrated in isolated interlobular arteries (160).

**Modulation of the Contribution of the Autoregulatory Mechanisms**

Despite obvious impact on the kinetics of autoregulation, little is known about whether and how the balance of the contributions of autoregulatory mechanisms is modulated. The most likely candidates for such modulating factors are those that are known to alter the strength of TGF and/or MR but do not interfere with the overall steady-state autoregulatory efficiency. Two factors characteristically fulfilling these criteria are ANG II and NO. Other potential modulators are the level of arterial pressure, sympathoadrenergic activation, endothelin, cyclooxygenase metabolites, and the status of salt and water balance.

**ANG II.** ANG II is a strong modulator of TGF, as shown by augmentation of TGF during infusion of ANG II (24, 82, 131, 165) and attenuation during ACE-inhibition (82, 131, 148, 183, 211), ANG II receptor antagonism (24, 105, 131, 183, 211), and genetic ablation of AT1A receptors (170). ANG II is also known to augment MR in renal (108) and extrarenal vessels (64, 142). Despite a strong vasoconstrictor effect on the baseline level of RBF, steady-state autoregulation is typically not affected by ANG II infusion (106), ACE-inhibition (7, 69, 145), nor ANG II receptor antagonists (1, 5, 17, 69, 145). However, the strength and relative contribution of MR to autoregulation and, thus presumably, the balance of the contributions of MR, TGF, and a third mechanism are not affected by reductions or elevations of ANG II plasma levels in dogs (99) (SF-20166) or rats (97) (Fig. 3A). In fact, in view of the solid stability of the relative contributions during infusion of ANG II, despite renal vasoconstriction and hypertension, one might even be tempted to speculate that ANG II could be involved in actively stabilizing the balance of autoregulating mechanisms.
NO. NO also strongly modulates TGF (89, 154, 193, 200, 212). Its influence is asymmetric, mitigating the vasoconstrictor response elicited by high tubular perfusion rates or NaCl concentrations but not affecting TGF at low perfusion rates (89, 154, 193, 212). Nevertheless, the inhibitory influence of NO includes the autoregulatory efficiency at the operating point, although only in a small range around this point (200). Although a constant level of NO would theoretically be sufficient to explain these observations, clamping studies have demonstrated that endogenous changes of NO during stimulation of TGF rather than the mere presence of NO are necessary for the attenuation of the TGF response (197). Consistent with this concept, macula densa cells acutely release NO on stimulation of TGF (112, 118, 119). The NO responsible is largely produced by nNOS in macula densa cells (154, 192, 210). Although NO has also been reported to attenuate MR in vessels from skin (63), myocardium (151, 158, 198), mesentery (150), spleen (25), and skeletal muscle (46, 93, 141), other studies failed to confirm such an effect at least in the skeletal muscle circulation (50, 51, 97, 184). The picture is even less consistent in the kidney. Although a mitigation of MR was observed in some in vitro preparations (23, 85, 95), other studies found the effect to be limited to the afferent and efferent arteriole (73, 86) or was completely absent (70, 219). Investigations in intact kidneys in vivo indicate that the attenuation of MR depends largely (179) or completely (97) on the presence of a functional TGF. Despite a strong and continuous dilator influence of endogenous NO on baseline RBF, steady-state autoregulation is typically not affected by inhibition of NO production (12, 14, 125).

The strong evidence for an attenuating influence of NO on TGF and variable effects on MR suggest a shift of the balance in favor of TGF in the absence of NO. However, transfer function analysis studies suggest a stronger MR and faster autoregulation during NO inhibition (179, 206, 207). Although transfer functions do not allow reliable determination of overall steady-state autoregulation and thus limit the estimation of the relative contribution, more direct investigation using step-response analysis (Fig. 3) confirmed the enhancement of strength and contribution of MR to overall RBF autoregulation (97, 215). Figure 3 also demonstrates that the shift in favor of MR during NOS-inhibition makes the overall response considerably faster. In addition, the speed of MR itself is accelerated in the absence of NO (Fig. 3) (97). The underlying mechanism of this suppression of MR by NO is unclear at present, although it appears to involve some interaction with TGF (97, 179). One tentative explanation for the predominance of MR in the absence of NO is that MR might naturally dominate the autoregulatory function, because it is both faster and located upstream to TGF and the third regulatory mechanism, so that it would minimize any error signal from reaching the latter mechanisms. One might speculate that in the normal animal the strength of MR is restrained to a more balanced contribution only due to interactions with TGF, the latter of which might be enhanced by NO. Gap junctions might be a potential target for both the interactions and modulation by NO. Interestingly, NO has been found to enhance gap junctional coupling in mesangial cells (216) and astrocytes (22), although an inhibitory influence of NO has also been reported in other settings (104, 157). Further studies will be necessary to clarify the underlying mechanism of the modulatory influence of NO and to determine whether the relevant NO derives from the macula densa or endothelium.

**Level of arterial pressure.** During elevation of arterial pressure above the resting level, the contribution of MR becomes larger, but only in the absence of NO (97), suggesting that pressure-dependent modulation of the balance of the autoregulatory mechanisms is muted by endogenous production of NO in the normal animal. Preliminary data suggest that during reduction of arterial pressure close to the lower limit of autoregulation, overall autoregulation and MR are reduced, TGF is diminished, and its contribution to RBF autoregulation lost (101), whereas the third regulatory mechanism gains more influence (96, 101). This is in line with previous findings of a reduced strength of TGF at lower arterial pressure (167, 175).

More work is needed to characterize further factors and conditions involved in modulating the strength and relative contribution of the autoregulating mechanisms and their potential physiologic and pathophysiologic relevance.

**Perspectives.** RBF autoregulation is due to the action of MR, TGF, and a third regulatory mechanism. The underlying cause of the third mechanism remains unclear to date. An appealing possibility is that it is mediated by P2X1-receptors, but this awaits experimental testing. The modulatory influences of NO and ANG II are also important but mainly operate through modulation of MR and TGF and are thus probably not separate entities.

MR requires < 10 s for completion in the renal circulation and usually follows first-order characteristics without prominent rate-sensitive components. TGF comprises a lag time of 15 s and a time constant of ~20 s so that it requires 30–60 s for completion and typically shows spontaneous oscillations at 0.025–0.033 Hz. The third regulatory component requires 30–60 s for completion. RBF and TGF resetting stretch out over 20–60 min and may pose a lower frequency limit for the operation of TGF (<0.001 Hz), which might be partially offset by the strengthening effect of pressure-induced modulation of proximal tubular reabsorption.

Due to these kinetic differences, the relative contribution of the autoregulatory mechanisms importantly determines the amount and spectrum of pressure fluctuations reaching glomerular and postglomerular capillaries and may thus impact on filtration, reabsorption, medullary perfusion, and hypertensive renal damage. Under resting conditions, MR contributes ~50% to overall RBF autoregulation, TGF 35–50%, and the third mechanism < 15% at resting arterial pressure. This balance among the autoregulating mechanisms is not fixed but subject to modulation. NO attenuates the strength, speed, and contribution of MR. In contrast, ANG II does not affect the balance of contributions.

Many open questions remain. Among them are the underlying cause(s) of the third regulatory mechanism and the roles of adenosine and ATP in TGF and overall RBF autoregulation. Whether the two questions may converge to the same answer is not yet clear. Other important issues are further factors modulating the balance among the autoregulatory mechanisms and the potential physiological and pathophysiological significance of imbalances. Of particular interest might be diseases with enhanced susceptibility to renovascular damage associated with augmented renal NO-production, that could depress the shield of the fast-acting MR, such as diabetic nephropathy (110), and genetic glomerulosclerosis (200a, 206, 209). A more
interdisciplinary topic reaching out beyond the renal hemodynamic field pertains to the different kinetics of MR in various tissues and preparations, the clarification of which might also contribute to the understanding of the dynamics and signaling pathways of smooth muscle contraction.

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