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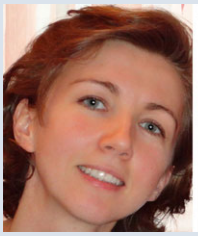
SYMPOSIUM REVIEW

A mathematical model of salt-sensitive hypertension: the neurogenic hypothesis

Viktoria A. Averina[1], Hans G. Othmer[1], Gregory D. Fink[2] and John W. Osborn[3]

[1] *Department of Mathematics, University of Minnesota, Minneapolis, MN, USA*
[2] *Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, USA*
[3] *Integrative Biology and Physiology, University of Minnesota, Minneapolis, MN, USA*

Abstract Salt sensitivity of arterial pressure (salt-sensitive hypertension) is a serious global health issue. The causes of salt-sensitive hypertension are extremely complex and mathematical models can elucidate potential mechanisms that are experimentally inaccessible. Until recently, the only mathematical model for long-term control of arterial pressure was the model of Guyton and Coleman; referred to as the G-C model. The core of this model is the assumption that sodium excretion is driven by renal perfusion pressure, the so-called 'renal function curve'. Thus, the G-C model dictates that all forms of hypertension are due to a primary shift of the renal function curve to a higher operating pressure. However, several recent experimental studies in a model of hypertension produced by the combination of a high salt intake and administration of angiotensin II, the AngII–salt model, are inconsistent with the G-C model. We developed a new mathematical model that does not limit the cause of salt-sensitive hypertension solely to primary renal dysfunction. The model is the first known mathematical counterexample to the assumption that all salt-sensitive forms of hypertension require a primary shift of renal function: we show that in at least one salt-sensitive form of hypertension the requirement is not necessary. We will refer to this computational model as the 'neurogenic model'. In this Symposium Review we discuss how, despite fundamental differences between the G-C model and the neurogenic model regarding mechanisms regulating sodium excretion and vascular resistance, they generate similar haemodynamic profiles of AngII–salt hypertension. In addition, the *steady-state* relationships between arterial pressure and sodium excretion, a correlation that is often erroneously presented as the 'renal function curve', are also similar in both models. Our findings suggest that salt-sensitive hypertension is not due solely to renal dysfunction, as predicted by the G-C model, but may also result from neurogenic dysfunction.



Viktoria Averina received an MS in mathematics from the University of Alaska, and is currently a PhD candidate in Applied Mathematics at the University of Minnesota. Her thesis research is focused on applying principles of mathematical modelling and sensitivity analysis to understanding the interactions between physiological systems in long-term blood pressure control. She is also a Principal Biomedical Research Scientist at Boston Scientific developing sensor algorithms for the detection of worsening heart failure. **John Osborn** received his PhD in physiology from the Medical College of Wisconsin in 1986 where he studied hormonal modulation of central sympathetic pathways with Dr Allen Cowley, Jr. He pursued postdoctoral studies with Dr Lawrence Schramm in biomedical engineering at Johns Hopkins School of Medicine where he studied spinal level control of the sympathetic nervous system. He joined the faculty at the University of Minnesota in 1988 where he is currently Professor and the Marvin and Hadassah Bacaner Endowed Chair in Cardiovascular Physiology and Director of Graduate Studies. His career has focused primarily on neural mechanisms for long-term control of arterial pressure.

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Corresponding author: J. W. Osborn, Department of Integrative Biology and Physiology, 2231 6th Street SE, 3–138 Cancer Cardiovascular Research Building, Minneapolis, MN 55455, USA. Email: osbor003@umn.edu

Abbreviations AngII, angiotensin II; AP, arterial pressure; BV, blood volume; BW, body weight; CO, cardiac output; ECFV, extracellular fluid volume; G-C, Guyton–Coleman (model); MCFP, mean circulatory filling pressure; NaI, sodium intake; NTS, nucleus tractussolitarius; R_{as}, arterial splanchnic resistance; R_{ar}, arterial extra-splanchnic resistance; RVLM, rostral ventrolateral medulla; SNA, sympathetic nerve activity; TPR, total peripheral resistance.

Overview: why do we need a new mathematical model of salt-sensitive hypertension?

Salt sensitivity of arterial pressure is a global health problem. It is estimated that 25% of the normotensive population is salt-sensitive and 50–75% of hypertensive patients exhibit an exaggerated arterial pressure response to increased salt intake (Weinberger, 1996). This is clinically significant since it is hypothesized that salt-sensitivity of arterial pressure is a stronger predictor of death and disability due to cardiovascular disease than arterial pressure itself (Weinberger, 1996). There are several definitions of salt sensitivity (Sanada *et al.* 2011) and here we define it as a steady-state increase in mean arterial pressure of more than 10 mmHg with a sustained 5-fold increase in sodium intake.

Why do we need mathematical models of hypertension? Computational models are useful in at least two important ways. First, since the causes of salt-sensitive hypertension are extremely complex, mathematical models can elucidate potential mechanisms that are experimentally inaccessible. Second, they generate novel hypotheses that are not immediately apparent from experimental studies. Moreover, when two models predict experimental observations equally well but under different hypotheses, it may provide guidance to the experimental community in designing experiments to distinguish between alternative paradigms.

Until recently, the only mathematical model for long-term control of arterial pressure was the model first introduced by Guyton and Coleman in 1967 (Guyton & Coleman, 1967). The core of this model is the relationship between renal perfusion pressure and sodium excretion, the so-called 'renal function curve', which acts as the primary long-term controller of arterial pressure (Guyton *et al.* 1972*a*). This model has been accepted by many investigators, and is presented in most physiology textbooks as the only explanation for the pathogenesis of hypertension. In this review we will we refer to it as the G-C model.

If the G-C model is generally accepted, then why do we need a new mathematical model? At the time the G-C model was developed, very little was understood about neural control of the circulation beyond the arterial baroreceptor reflex. However, a large number of studies over the last five decades suggest that the sympathetic nervous system plays a much more important role in salt-sensitive hypertension than previously recognized (Grassi *et al.* 2008; Esler, 2010; Malpas, 2010). In particular, several recent reports suggest that a well-established animal model of salt-sensitive hypertension, the AngII–salt model, is sympathetically driven independently of neurally mediated changes in kidney function. As such, these experimental findings are incompatible with the G-C model. We sought to determine whether we could construct a predictive mathematical model that did not limit the cause of salt-sensitive hypertension solely to primary renal dysfunction (Averina *et al.* 2012). We refer to this computational model as the neurogenic model.

In this Symposium Review we discuss how, despite fundamental differences between the G-C model and the neurogenic model regarding mechanisms regulating sodium excretion and vascular resistance, they generate similar haemodynamic profiles of AngII–salt hypertension.

In addition, the *steady-state* relationships between arterial pressure and sodium excretion, a correlation that is often erroneously presented as the 'renal function curve', are also similar in both models. Our findings suggest that salt-sensitive hypertension may not be due solely to renal dysfunction, as predicted by the G-C model, but may also result from neurogenic dysfunction. We will conclude by discussing new hypotheses generated by the neurogenic model and our plans for model expansion in the future.

The AngII–salt experimental model of salt-sensitive hypertension

One of the most commonly studied animal models of salt-sensitive hypertension is the AngII-induced model. The mechanism(s) whereby chronic administration of AngII causes hypertension has been debated for decades since this hormone has vascular, renal and neural actions that can theoretically cause hypertension. However, one thing that is generally agreed upon is that the magnitude of AngII-induced hypertension is directly related to the prevailing level of dietary salt intake. A typical example of this is illustrated in Fig. 1*A*. In this study, the mean arterial pressure (MAP) response to chronic administration of

AngII to rats consuming a low salt (0.1% NaCl) diet was minimal, whereas the same dose of AngII caused progressively greater increases in rats consuming normal (0.4% NaCl) and high (2.0% NaCl) diets.

The conventional explanation for this finding is that AngII stimulates sodium and water reabsorption by the kidney leading to increased blood volume; and arterial pressure rises as a direct consequence of the increased volume. Based on this explanation, the greater increase in arterial pressure in animals consuming a high salt diet is due to a larger degree of sodium retention leading to greater blood volume expansion. This is classically referred to as the 'volume loading' hypothesis of hypertension as predicted by the G-C model.

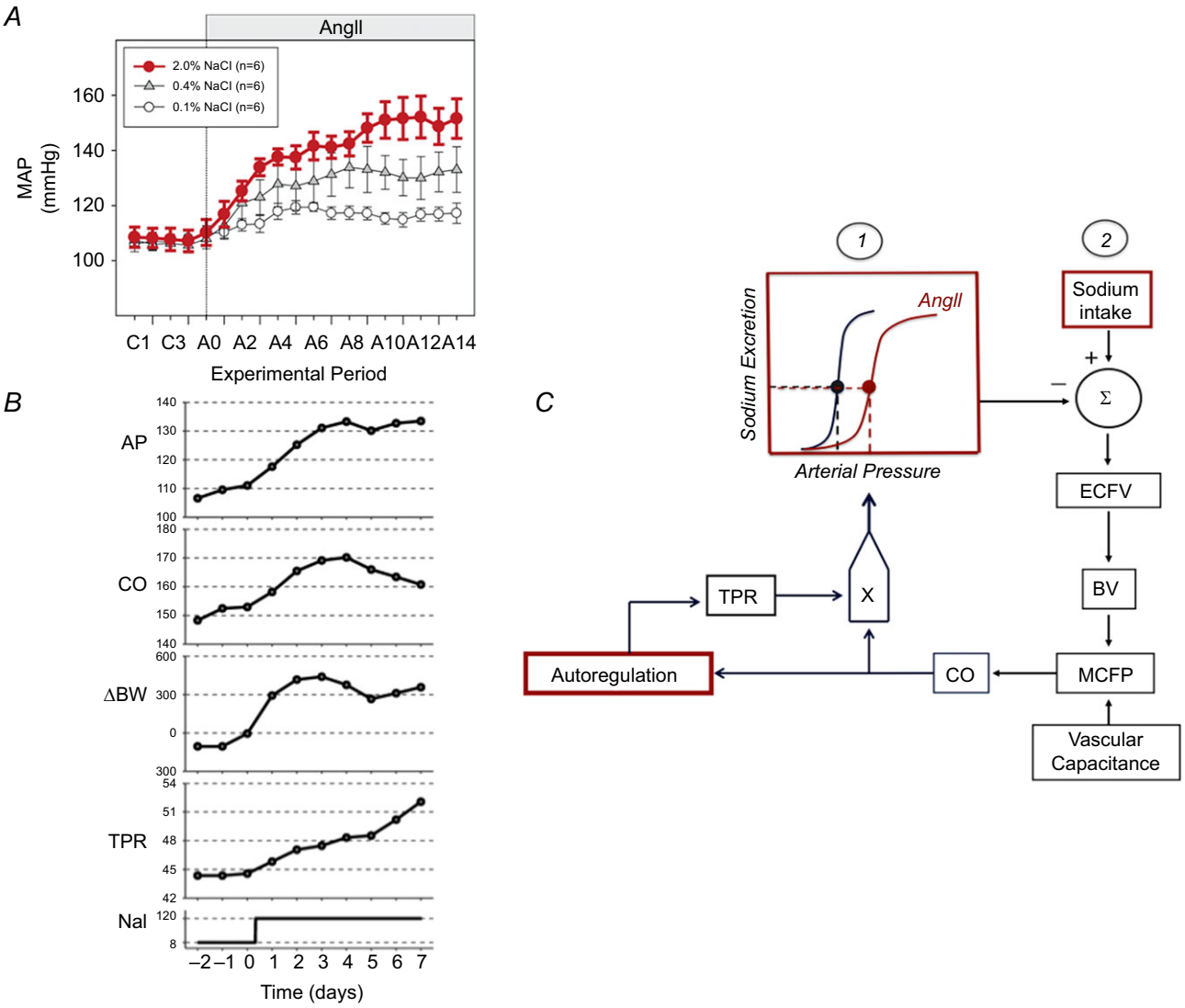

Figure 1.
A, the response of mean arterial pressure (MAP) to angiotensin II (AngII) administration (150 ng kg^{-1} min^{-1}) in Sprague–Dawley rats consuming low (0.1%), normal (0.4%) or high (2.0%) salt diets. Values are 24 h averages measured by radiotelemetry. Figure from Osborn *et al.* (2011). *B*, responses of arterial pressure (AP; mmHg), cardiac output (CO; ml min^{-1} kg^{-1}), body weight (BW; g), total peripheral resistance (TPR; mmHg kg^{-1} min^{-1}) to increased salt intake (NaI; mequiv) in conscious dogs with 'clamped plasma AngII'. Figure from Averina *et al.* (2012). *C*, simplified representation of the G-C model explanation of the relationship between arterial pressure, sodium excretion and sodium intake in AngII–salt hypertension. The two determinants of the long-term level of arterial pressure are: (1) the renal function curve and (2) sodium intake. The combination of a rightward shift of the renal function curve by AngII and increased sodium intake summates to increase extracellular fluid volume (ECFV), blood volume (BV), mean circulatory filling pressure (MCFP) and therefore cardiac output (CO). Cardiac output directly influences arterial pressure but also gradually increases total peripheral resistance as a result of autoregulation.

The haemodynamic profile of AngII–salt hypertension

The role of blood volume expansion and its impact on haemodynamic function in AngII–salt hypertension has been studied in chronically instrumented conscious dogs (Krieger *et al.* 1989, 1990). In this elegant study, haemodynamic variables (arterial pressure and cardiac output) and total body weight were measured continuously in dogs in which plasma AngII was 'clamped' at physiological levels by intravenous infusion. Total body weight was used as a surrogate for total body water to track dynamic changes in body fluid volume over time. Following a control period, daily sodium intake was increased and haemodynamic and body weight changes were measured.

As shown in Fig. 1*B*, the salt-induced increase in arterial pressure was correlated with an early increase in total body weight (i.e. total body water) and cardiac output. This was followed by a delayed rise in total peripheral resistance (TPR) and a subsequent return of cardiac output towards control levels. The steady-state profile of this classic 'volume loading' haemodynamic profile is similar to what has been reported in humans with established essential hypertension; that is, increased arterial pressure and total peripheral resistance with normal or near normal cardiac output.

Mechanisms of AngII–salt hypertension: the G-C model

The core concept of the G-C model is shown in Fig. 1*C*. As stated in the excellent monograph by Guyton, this model dictates that there are 'two determinants' of the long-term level of arterial pressure; (1) the chronic renal function curve and (2) net sodium (and water) intake (Guyton, 1980). In this model, the renal function curve is the primary controller of renal sodium excretion, and therefore plays a major role in the maintenance of sodium balance. The pressure natriuresis relationship is believed to be an intrinsic function of the kidney although it is modulated by external hormonal and neural inputs. More importantly, " . . . the long-term level of arterial pressure cannot be changed in any way other than by changing one or both of these two determinants"(Guyton, 1980). In other words, the G-C model dictates that at any given level of salt (and water) intake *all* forms of hypertension are the result of a *primary* shift of the renal function curve to a higher operating pressure.

Figure 1*C* illustrates the G-C model explanation of the haemodynamic profile of AngII–salt hypertension. AngII causes a primary shift of the renal function curve to the right (i.e. higher operating pressure) as a result of the actions of AngII on renal function. This is labelled in Fig. 1*C* as '1' according to the G-C model. The immediate consequence of this is a reduction of urinary sodium excretion since arterial pressure at this point is still at a normal level (i.e. below the new set point of the renal function curve). Salt intake is also increased in the AngII–salt protocol, which is labelled as '2'. The combination of a shift of the renal function curve and increased salt intake increases extracellular fluid volume (ECFV) and therefore blood volume. Blood volume expansion results in subsequent increases in mean circulatory filling pressure (MCFP) and cardiac output (CO), which is initially responsible for increased arterial pressure. Finally, another key feature of the G-C model is that the increase in total peripheral resistance is mediated by 'whole body autoregulation', secondary to overperfusion of tissues from the elevated cardiac output. As with the renal function curve, this is an intrinsic property of the vasculature and, as such, is not dependent on neural or hormonal controllers.

In summary, the G-C model predicts that the haemodynamic profile of AngII–salt hypertension is due to a *primary* shift of the renal function curve, initiating a sequence of events driven by increased *blood volume*, which lead to the temporal patterns of cardiac output and total peripheral resistance shown in Fig. 1*B*. It is important to keep in mind that the G-C model dictates that this is the *only* cause for hypertension and that the haemodynamic profile is independent of neural control of cardiovascular function.

Recent studies of AngII–salt hypertension are inconsistent with the G-C model

In several recent studies we have reported that, when AngII is administered to rats on a high salt diet, the resulting hypertension is caused, in part, by delayed activation of the sympathetic nervous system (King & Fink, 2006; Osborn *et al.* 2007, 2011; Osborn & Fink, 2010; Toney *et al.* 2010). Theoretically these findings could be consistent with the G-C model since neurogenic hypertension may occur as a result of increased sympathetic nerve activity (SNA) to the kidney which would shift the renal function curve to a higher operating pressure as described above (Guyton, 1980).

However, long-term continuous direct recording of renal SNA in conscious rats revealed that it is transiently *decreased* in AngII–salt rats, rather than increased (Yoshimoto *et al.* 2010). Furthermore, renal denervation did not affect the development of AngII–salt hypertension (King *et al.* 2007), and hypertension was not associated with chronically increased blood volume (King & Fink, 2006). Furthermore, splanchnic SNA seemed critical to AngII–salt hypertension since denervation of the splanchnic vascular bed attenuated the development of hypertension (King & Fink, 2006; King *et al.* 2007),

probably by reducing sympathetically mediated changes in both splanchnic vascular resistance and capacitance (Kuroki *et al.* 2012).

We have also found that interventions that target the brain specifically attenuate or abolish the neurogenic phase of AngII–salt hypertension. Lesion of forebrain sites responsive to AngII and osmolality, the subfornical organ and the organum vasculosum of the lamina terminalis, attenuate hypertension in AngII–salt rats (Osborn *et al.* 2012; Collister *et al.* 2013). More recently, we reported that chronic intracerebroventricular administration of the sodium channel blocker benzamil completely reversed the neurogenic phase of AngII–salt hypertension (Osborn *et al.* 2014).

Taken together, these studies suggest that AngII–salt hypertension in the rat is neurogenically driven by activation of sodium-dependent sympathoexcitatory pathways in the brain that do not, as predicted by the G-C model, target the kidneys but rather the splanchnic vascular bed. Therefore, this form of hypertension cannot be due to a primary shift of the renal function curve and subsequent blood volume expansion. This led us to develop a mathematical model that would help explain these new findings.

A new mathematical model of salt-sensitive hypertension: the neurogenic hypothesis

The goal of our mathematical modelling was to show that one can reproduce the same physiological observations under quite different modelling assumptions. In such a case one could conclude that either set of assumptions may hold true in the actual circulation. Thus, we created a model that can simulate the haemodynamic profile of AngII–salt hypertension based *either* on the assumptions of the G-C model or on assumptions derived from more recent experimental findings that support the emerging neurogenic hypothesis. In particular, we focused on regulation of two key variables that affect arterial pressure: sodium excretion and total peripheral resistance.

Key question 1: is pressure natriuresis the primary determinant of the renal response to increased salt intake?

It is a well-established empirical fact that urinary sodium excretion is tightly regulated to match sodium intake under steady-state conditions. But critical gaps remain in our understanding of the mechanisms responsible for this relationship(Bie, 2009). Although renal perfusion pressure is one important factor influencing renal sodium excretion, a necessary link between mean arterial pressure and sodium excretion has been questioned (Seeliger *et al.* 2004; Bie, 2009). In particular, at steady state, healthy kidneys are capable of excreting a wide range of sodium intakes with no measureable change in mean arterial pressure. Indeed, a recent study of circadian rhythms of cardiovascular and renal function in conscious dogs showed that urinary sodium excretion was increased during time intervals when arterial pressure was the lowest (Mochel *et al.* 2014).These findings raise the question: could the haemodynamic changes that occur in salt-sensitive hypertension be predicted by a model of circulatory regulation that did not include the pressure natriuresis mechanism?

In the mathematical model we describe here, sodium excretion is made to exactly match changes in sodium intake in one of two distinct ways: either in response to changes in arterial pressure (i.e. pressure natriuresis), or by undefined mechanisms independent of arterial pressure (i.e. pressure-independent natriuresis). Note that the latter approach for current purposes merely represents a lumped function of all sodium excretory mechanisms other than arterial pressure.The choice of the former represents the pressure natriuresis of the G-C model and the choice of the latter represents the neurogenic model. The overall concept is that, in the G-C model, the renal function curve is operating in series with other pressure regulators so the latter work by affecting the pressure natriuresis mechanism. In contrast, in the neurogenic model, a number of potential regulators operate in parallel to regulate sodium excretion.

Key question 2: what mediates increased total peripheral resistance in AngII–salt hypertension?

Acceptance of the G-C model as a valid mathematical description of the circulation is based, in part, on the fact that it accurately predicts haemodynamic responses to numerous physiological perturbations, including changes in salt intake and/or AngII administration (Guyton, 1980). These haemodynamic responses in the G-C model are driven mainly by autoregulatory adjustments to vascular tone (i.e. total peripheral resistance) with relatively little contribution by neural controllers.

Our studies of AngII–salt hypertension in the rat demonstrated that although renal SNA was transiently decreased, lumbar (mainly muscle) SNA was maintained (Yoshimoto *et al.* 2010). Furthermore, splanchnic SNA seemed critical to AngII–salt hypertension since denervation of the splanchnic vascular bed attenuated hypertension development (King & Fink, 2006; King *et al.* 2007). This finding is consistent with our observations that splanchnic vascular resistance is increased and total vascular capacitance is decreased in AngII–salt rats, and that both of these responses are reversed by acute ganglionic blockade (King & Fink, 2006; Kuroki *et al.* 2012). Therefore, splanchnic denervation

probably affects hypertension development by reducing sympathetically mediated changes in both splanchnic vascular resistance and capacitance (Osborn *et al.* 2011). Finally, we have reported that in rats both AngII and high salt intake are required to induce elevated SNA, while either factor alone does not trigger a sympathetic response (King *et al.* 2008). Since we are attempting to model AngII–salt hypertension, here we assume that the long-term level of SNA is driven by a combination of increased sodium intake and circulating AngII.

In our mathematical model we describe arterial resistance control as driven by either the autoregulatory response to overperfusion (i.e. autoregulation) or the sympathetic nervous system. The choice of the former represents the whole-body autoregulation hypothesis of the G-C model and the choice of the latter represents the neural control of the neurogenic model.

Basic features of the model

The details of the mathematical model have been recently described elsewhere (Averina *et al.* 2012). Figure 2 summarizes our approach. In simple terms, the aim of our modelling exercise was to demonstrate that one can reproduce both the hypertensive haemodynamic profile and pressure natriuresis relationship under very different assumptions about the primary mechanism regulating sodium excretion.

The circulatory subsystem used in both the G-C model (Fig. 2*A*) and the neurogenic model (Fig. 2*B*) is the same. It is based on the lumped-parameter Windkessel approach widely used in cardiovascular modelling. Lumped parameter models are used on both short time scales, such as the response to haemorrhage, baroreceptor stimulation and postural change (Ursino *et al.* 1994; Ursino, 1998; Olufsen *et al.* 2005), and long-term scales such as the G-C model (Guyton *et al.* 1972*b*). In our model of the circulatory system, total blood volume is distributed among four capacitive vascular compartments: the arteries, the veins of the splanchnic organs, the veins of extra-splanchnic organs, and the large veins. The two compartments representing the systemic vascular beds are connected in parallel. One of these two compartments is assumed to have a higher compliance than the other. Since splanchnic organs have larger vascular compliance than other regions (Rothe, 1983), we call the former compartment 'splanchnic' and the latter 'extra-splanchnic'. The pulmonary circulation is omitted and the heart is represented by a continuous non-pulsatile pump which moves blood from the venous

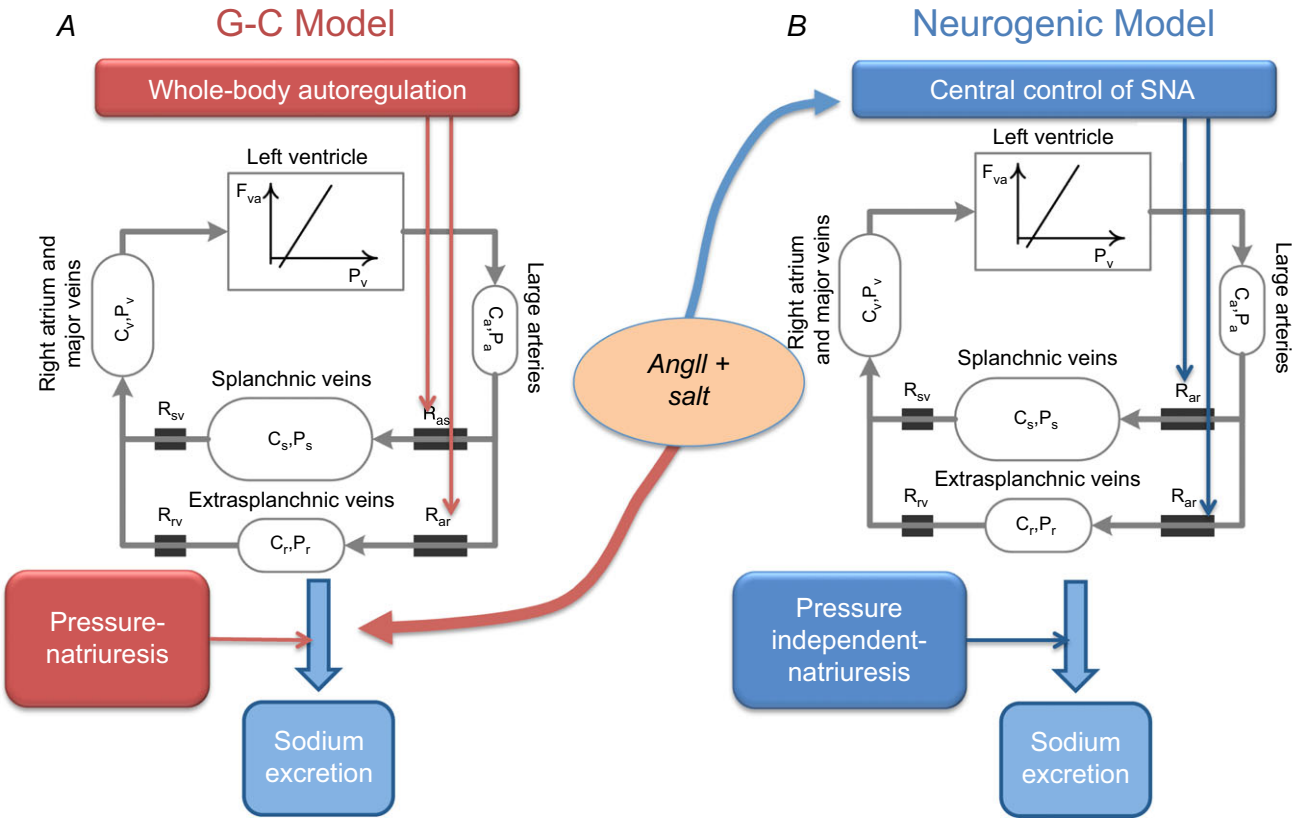

Figure 2.
Schematic representation of the similarities and differences between the G-C (*A*) and 'neurogenic' (*B*) models. See text for details.

to the arterial side of systemic circulation. The flow generated by the pump is impeded by arterial and venous resistances located around each of the two parallel vascular bed compartments.

In the G-C model, the assumption is that sodium excretion is ultimately determined by arterial pressure (i.e. pressure natriuresis) and vascular resistance is a function of 'whole body autoregulation'. In the neurogenic model the assumption is that sodium output is independent of arterial pressure (i.e. pressure independent natriuresis) and that vascular resistance is determined by sympathetic nerve activity (SNA). In the G-C model, hypertension caused by AngII in combination with high salt intake is due to a *primary* shift in the pressure natriuresis mechanism (i.e. renal function curve) to a higher operating pressure. In contrast, AngII–salt hypertension in the neurogenic model is due to *primary* activation of central sympathetic drive.

Model simulations of the haemodynamic profile of AngII–salt hypertension

Our first key finding was that both the G-C model and the neurogenic model generate similar haemodynamic profiles in response to the same input (i.e. increased AngII and sodium intake). Figure 3*A* shows the key model simulations for the G-C (grey line) and neurogenic (black line) models as compared to the haemodynamic profile of AngII–salt hypertension in dogs (Fig. 3*B*). Shown at the bottom of Fig. 3*A* are the two forcing functions of

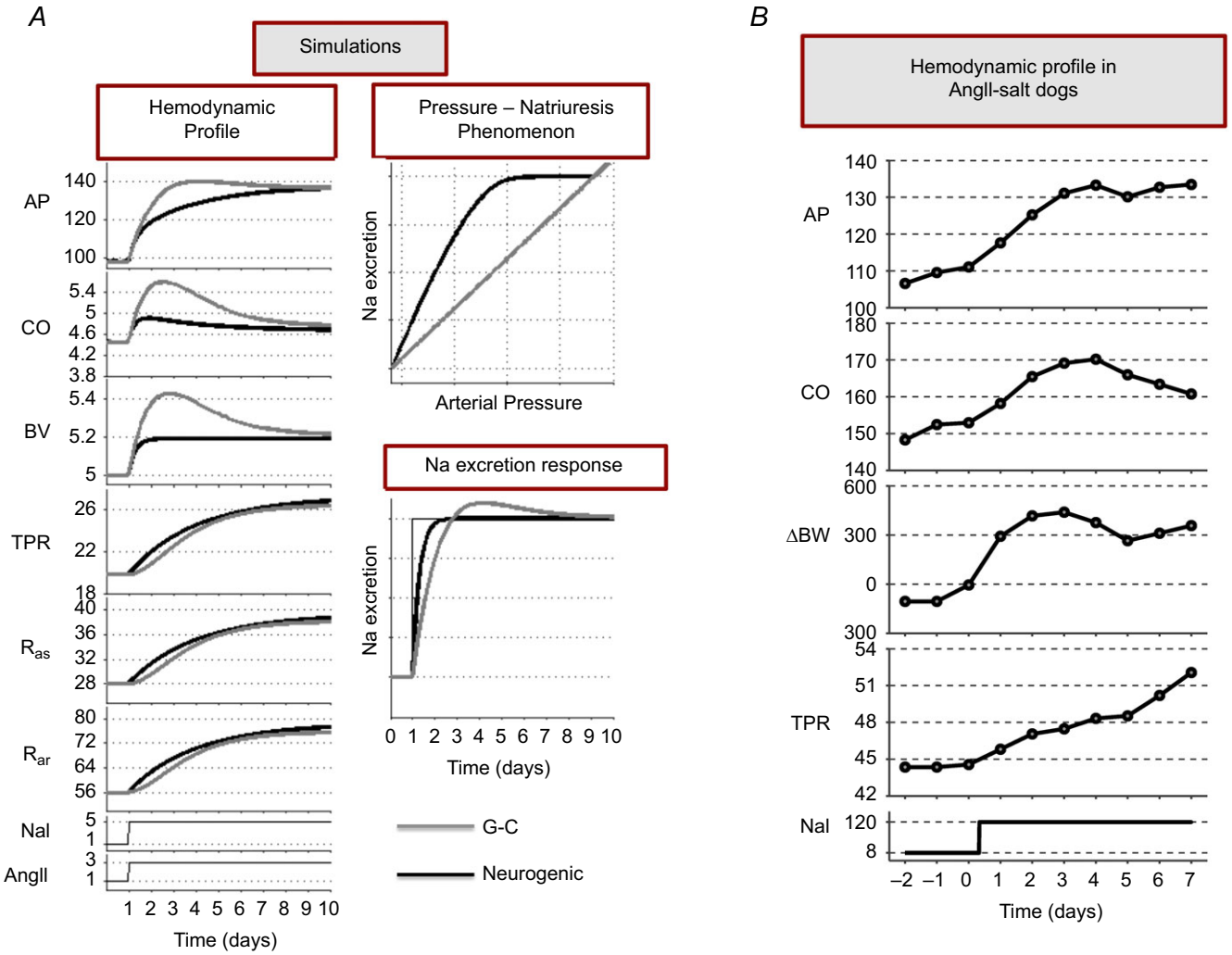

Figure 3.
A, simulations for the G-C model (grey lines) and the neurogenic model (black lines) produced by our mathematical model (Fig. 2). Responses shown are; arterial pressure (AP), cardiac output (CO), blood volume (BV), total peripheral resistance (TPR), arterial splanchnic resistance (R_{as}), arterial extra-splanchnic resistance (R_{ar}), sodium intake (NaI) and normalized plasma angiotensin II (AngII). Sodium excretion responses are also shown. B, haemodynamic profile of AngII–salt hypertension in dogs (same as Fig. 1*B*) to be compared to the simulation results in *A*.

the model; a 5-fold increase in sodium intake (NaI) and a 3-fold increase in plasma AngII.

It is important to note that our simulation of the G-C model effectively reproduced the haemodynamic profile of the original Guyton–Coleman model (Guyton & Coleman, 1967; Guyton, 1984). Specifically, the initial increase in arterial pressure (AP) was due to a transient increase in blood volume (BV) and cardiac output (CO). This was followed by a gradual increase in total peripheral resistance (TPR) and a near normalization of CO to the steady state. More importantly, although the transient responses were not identical, the neurogenic model generated a haemodynamic profile similar to the G-C model. The initial increase in CO and BV were followed by increased TPR and, at steady state, haemodynamics in both models were identical.

Model simulations of the pressure natriuresis relationships of AngII–salt hypertension: the chronic pressure natriuresis *mechanism* vs. pressure natriuresis *correlation*

Our second key finding, as seen in the right panel of Fig. 3*A*, was that both the G-C model and the neurogenic model generated similar chronic pressure natriuresis relationships. As seen in the right panel of Fig. 3*A*, the pressure natriuresis relationship and sodium excretion responses of our G-C model was similar to the Guyton–Coleman model. More importantly, a positive *relationship* between arterial pressure and sodium excretion was observed in the neurogenic model despite the lack of a pressure natriuresis *mechanism* in the model.

The steady-state relationship between arterial pressure and sodium excretion is often presented as a 'chronic renal function curve' despite the fact that this relationship is not necessarily causal in nature. This is illustrated in Fig. 4. The steady-state relationship between sodium intake and arterial pressure is easy to establish and graph as shown in Fig. 4*A*. By definition, salt resistant subjects show little to no increase in arterial pressure over a wide range of sodium intake whereas salt-sensitive subjects will exhibit direct relationships of varying strengths between salt intake and arterial pressure.

The argument has been made that, since the relationship shown in Fig. 4*A* is measured at steady state, then the graph can be rotated as shown in Fig. 4*B* (DeClue *et al.* 1978). Also, since at steady state sodium excretion must equal sodium intake, this variable can be shown on the *y*-axis. Although these assumptions are correct, the graph shown in Fig. 4*B*, which is the 'chronic pressure natriuresis relationship', is often misunderstood to represent a *cause–effect* relationship between arterial pressure and sodium excretion, which is not correct. In other words, the graphical relationship shown in Fig. 4*B* is presented as a 'chronic renal function curve' which is not necessarily the case. This misleading presentation reinforces the concept that hypertension is 'caused' by a shift in the renal function curve, i.e. that a shift in the renal function curve is *necessary* to attain sodium balance at elevated levels of arterial pressure (Guyton, 1990).

The results of the neurogenic model simulation in which the chronic pressure natriuresis *relationship* is shifted to higher pressures, despite the lack of a pressure natriuresis *mechanism*, underscores a very important point. That this *must* happen in hypertension is obviously true just as the arterial baroreceptor reflex is shifted in hypertension (Barrett & Malpas, 2005). Therefore, it seems likely that resetting of both of these relationships is an *adaptation* to hypertension, rather than its cause. In fact, there is no dispute that *all* pressure controlling system must be reset in hypertension. The key question is whether this shift is *primary* (i.e. causes hypertension) or *secondary* (i.e. is caused by hypertension).

Addressing the issue of primary *vs.* secondary resetting of long-term pressure control systems is *the* single most important question to answer if we are to unravel the causes of long-term elevations of arterial pressure. Many investigators have accepted the G-C model as the most logical explanation for the pathogenesis of hypertension, based on the concept of primary resetting of the renal function curve. Since the model was developed prior to the avalanche of studies on autonomic control of cardiovascular function over the last few decades, this was a logical explanation at that time. This Symposium Review, however, demonstrates that it is no longer the *only* logical explanation. The neurogenic model is the first mathematical model to simulate the same haemodynamic

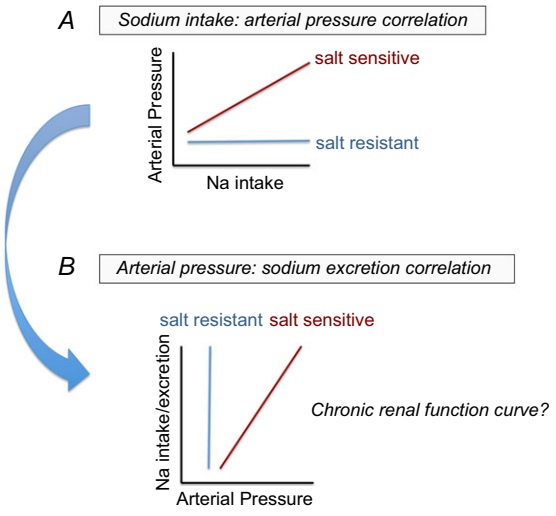

Figure 4.
Schematic representation of the steady-state relationship between (*A*) sodium (Na) intake and arterial pressure and (*B*) arterial pressure and sodium excretion. See text for details.

profile and pressure natriuresis correlations as the G-C model under a new set of assumptions. Although this model is still in the early stages and is not meant as a replacement for the G-C model, it is consistent with experimental studies and suggests the possibility that salt-sensitive hypertension can be of neurogenic origin in the absence of primary alterations in renal function.

Future directions: modelling brainstem networks that generate the 'AngII–salt sympathetic signature'

We have previously described the 'AngII–salt sympathetic signature' as it relates to the pathogenesis of hypertension in this model (Fig. 5). Based on several studies from our group, this experimental model is characterized by an increase in splanchnic SNA, transiently decreased renal SNA and no change in SNA to the skeletal muscle vascular bed (Osborn & Fink, 2010; Yoshimoto *et al.* 2010). We hypothesize that this pattern of regional SNA in AngII–salt hypertension results in a shift of blood volume from the highly compliant splanchnic vascular bed to the arterial compartment. We propose that this sympathetic pattern is driven by the actions of AngII on osmotically sensitive pathways in the brain that regulate sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM). The inset in Fig. 5 illustrates our current hypothesis regarding descending excitatory inputs to sympathetic premotor neurons for the splanchnic, renal and lumbar sympathetic nerves, as well as inhibitory baroreceptor inputs from the nucleus tractussolitarius (NTS). We hypothesize that differential control of splanchnic, renal and lumbar SNA is the result of differences in these excitatory and inhibitory inputs. A computational model of this network is currently underway.

Physiological and clinical relevance of the neurogenic model

The neurogenic model is based on the studies in which salt intake is increased in animals receiving exogenously administered AngII. One could argue that, since increased salt intake suppresses AngII under normal physiological conditions, the model is not physiologically relevant for human hypertension. While there is no single experimental animal model that fully mimics human essential hypertension, is there a human physiological condition under which AngII, plasma sodium and sympathetic nerve activity are increased chronically? The answer is yes; this occurs during chronic water deprivation.

Water deprivation is an environmental stress in which physiological control systems are critical to the

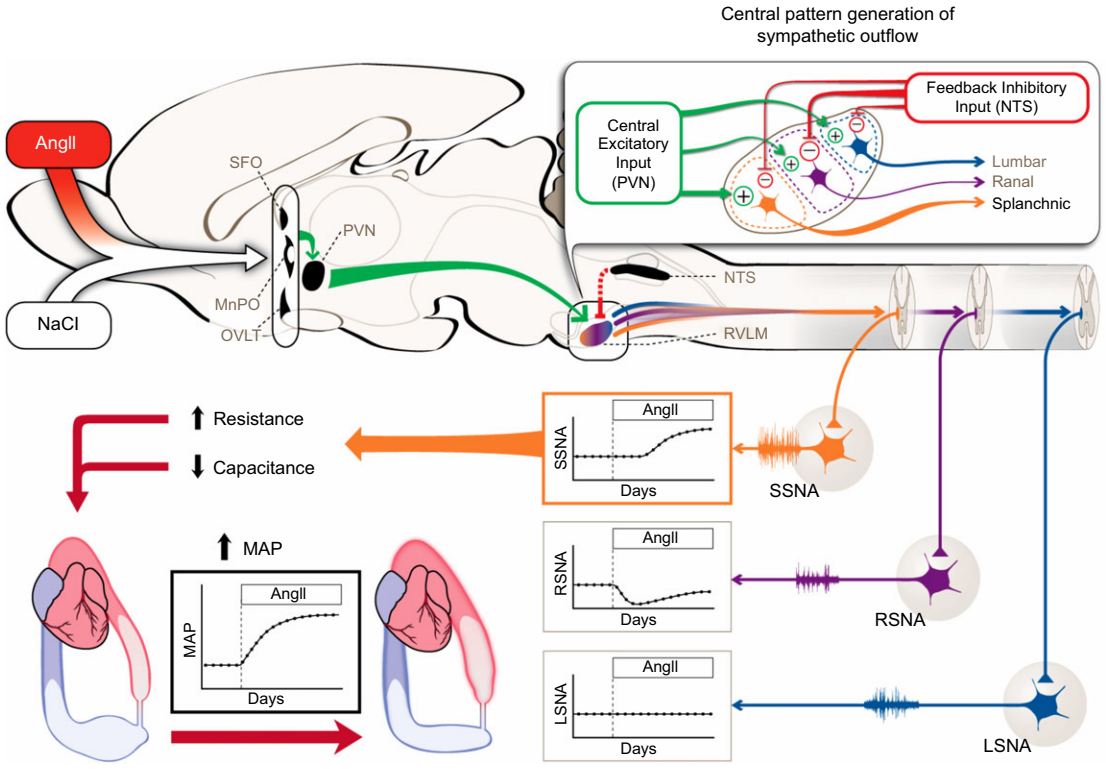

Figure 5.
Hypothetical mechanisms responsible for generation of the 'AngII–salt sympathetic signature'. Inset box illustrates current efforts to model brainstem networks that generate this differential pattern of sympathetic activity. Figure adapted from Osborn *et al.* (2011).

maintenance of body fluid homeostasis and perfusion of one of the most important organs for survival – the brain. We hypothesize that water deprivation increases plasma AngII, which acts on forebrain osmosensitive sites, to amplify the effects of increased plasma osmotically on central sympathetic pathways in the brain. More specifically these AngII-modulated osmotic pathways are responsible for increased SNA to the splanchnic vascular bed specifically. This results in neurogenic splanchnic venous and arteriolar constriction, which acts to mobilize blood from this highly compliant vascular bed to the arterial compartment to maintain arterial pressure and cerebral perfusion.

What is the clinical relevance of this response in relation to salt-sensitive hypertension? We hypothesize that the same interactions of plasma AngII with osmosensitive sympathetic pathways in the brain, which operate under conditions of water deprivation, are dysfunctional in salt-sensitive individuals such that they are not able to suppress SNA in response to increased salt intake.

This neurogenic hypothesis is supported by the work of Krieger and colleagues in their salt-loading haemodynamic studies in dogs. As presented earlier, the haemodynamic profile of the AngII–salt dog model (Krieger *et al.* 1989, 1990) is consistent with the G-C model. However, another study from this group, in which the identical salt-loading protocol was conducted in normal dogs in which plasma AngII was not clamped, is not consistent with the G-C model (Krieger *et al.* 1990). The G-C model would predict that salt-induced changes in arterial pressure in normal dogs are negligible because of the powerful ability of the kidneys to excrete the sodium load and maintain blood volume at normal levels. However, blood volume and cardiac output increases in response to salt loading in normal dogs (Krieger *et al.* 1990) were identical to those observed in dogs in which plasma AngII–salt was clamped by exogenous administration of the peptide (Krieger *et al.* 1989, 1990). However, normal dogs were 'salt-resistant' as a result of decreased total peripheral resistance.

These findings are important for two reasons. First, they demonstrate that normotensive dogs (i.e. normal kidney function) exhibit increased blood volume and cardiac output in response to increased salt intake. Second, although salt loading increased cardiac output in normotensive dogs, 'whole body autoregulation' was not observed and vascular resistance did not increase. Taken together, these studies (Krieger *et al.* 1989, 1990) demonstrate that the haemodynamic basis of AngII–salt hypertension in the dog is *not* due to primary renal dysfunction, which results in blood volume expansion, increased cardiac output and whole body autoregulation. Rather, these studies show that salt-induced hypertension in dogs with 'clamped' plasma AngII is the result of impaired vasodilatory response to salt intake and increased blood volume. We hypothesize that this impaired vasodilatory response is due to the inability to suppress plasma AngII, resulting in modulation of osmosensitive pathways in the brain that control sympathetic nervous system activity.

This hypothesis is consistent with other studies in rodents, e.g. chronic salt loading results in identical increases in blood volume and cardiac output in Dahl salt-resistant and Dahl salt-sensitive rats (Greene *et al.* 1990). However, Dahl salt-resistant rats remain normotensive as a result of reduced vascular resistance whereas Dahl salt-sensitive rats have an impaired vasodilatory response to increased salt intake. Finally, some studies in humans are consistent with these animal studies in dogs and rats. Whereas chronic increases in salt intake result in increased blood volume, reduced vascular resistance and no change in arterial pressure in normotensive salt-resistant humans, salt-sensitive subjects fail to vasodilate in response to salt induced increase in blood volume and cardiac output (Sullivan & Ratts, 1983). This similarity of these haemodynamic responses to increased salt intake in rodent and canine models andin humans with salt-sensitive hypertension suggests that, although dogs were used for development of the G-C model, and rats were used for development of neurogenic model, the fundamental physiological responses to increased salt intake are similar across species.

How are the above studies consistent with the neurogenic model? We hypothesize that increased salt intake normally suppresses plasma AngII and, therefore, reduces the AngII input to osmotically driven sympathoexcitatory pathways in the brain. This results in reduced sympathetic activity and vasodilatation (both venous and arterial) to accommodate blood volume expansion thereby maintaining normal arterial pressure under chronic salt loading conditions. We hypothesize that this response is impaired in salt-sensitive individuals resulting in hypertension. This could result from either an inability to suppress plasma AngII in response to increased salt intake, or impaired responsiveness of osmosensitive sympathoexcitatory pathways to AngII signalling mechanisms. This would result in an inappropriately high level of sympathetic activity during periods of blood volume expansion induced by a high salt intake. Moreover, this would occur in the presence of normal plasma AngII (impaired AngII response) or even suppressed plasma AngII concentration (impaired neural response to AngII). These hypotheses remain to be tested by further experimental studies. Finally, although the neurogenic model is in its early stages, it provides a platform the development of additional neurogenic models, which can incorporate data from past and future experimental studies of neurogenic cardiovascular diseases such as hypertension.

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Additional information

Competing interests

None declared

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