Minireview

Could hypertension possibly be adaptive?

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SUMMARY:

1. We believe that the ultimate goal of cardiovascular regulatory mechanisms is not the regulation of arterial blood pressure (BP) but the maintenance of tissue blood flows commensurate with metabolic requirements. Thus, elevated BP can potentially contribute to optimizing tissue blood flows under select circumstances; for example, when there are primary defects in autoregulation of tissue blood flows.

2. The hypothesis that a primary defect in autoregulation of tissue blood flows might be responsible for the development of hypertension is presented. It is argued that in this context, at least part of the rise in BP might be reflexly driven by a ‘metaboreflex’, a homeostatic mechanism acting to regulate tissue blood flows.

3. We argue that in the context of primary defects in autoregulation of tissue blood flows, the ability to generate and sustain a hypertensive phenotype increases the life span of species; i.e., if it were not for this adaptive hypertensive phenotype, death due to circulatory failure would occur much earlier.

4. Experimental and clinical evidence that indirectly support the hypothesis is briefly reviewed, and a means for testing this hypothesis is suggested.

Key words: autoregulation, blood flow, blood pressure, homeostasis, metaboreflex, sympathetic nervous system

List of abbreviations:

BP – blood pressure; MAP – mean arterial pressure; MSNA – muscle sympathetic nerve activity; SNA – sympathetic nerve activity; TPR – total peripheral resistance
INTRODUCTION

Despite years of intensive research, the ultimate cause of nearly 90% of clinical hypertension remains unknown even after extensive clinical investigation for an underlying cause (primary hypertension). In clinical practice, primary hypertension is defined as a resting systemic arterial blood pressure (BP) consistently ≥ 140/90 mmHg when measured over 2-3 weeks or longer and for which an underlying cause is not obvious despite detailed clinical and laboratory evaluation. It has come to be increasingly viewed as one manifestation of a heterogeneous syndrome that develops when one or more of several risk factors including increasing age, abdominal obesity, insulin resistance, dyslipidemia, psychologic stress, chronic cigarette smoking, interact with the genetic endowment of an individual over a variable and possibly very long time scale of years to decades to result in structural changes in the cardiovascular system and a sustained increase in systemic vascular resistance.

A meta-analysis concluded that, throughout middle and old age, BP is strongly related to vascular and all cause mortality down to a BP of 115/75 mmHg with no evidence of a threshold. However, in a reanalysis of data from the Framingham Heart Study, Port et al. predicted that risk is unrelated to systolic pressure up to the 70th percentile for each age and sex but increased sharply with BP above the 80th percentile. While BP lowering therapy has been demonstrated to reduce morbidity and deaths associated with chronically elevated BP, this has not been uniformly the case, and it leads one to suspect that hypertension might be adaptive under certain conditions. For example, a systematic review of 46 randomized trials involving 4282 pregnant women did not find enough
evidence of benefit in lowering BP in mild to moderate hypertension. 7 Antihypertensive therapy had an insignificant effect compared to no antihypertensive drug or placebo in terms of the following outcome measures: risk of preeclampsia, risk of the baby dying, preterm birth, small for gestational age babies, although it halved the risk of severe hypertension in 19 trials. 7 What might be the physiologic mechanisms responsible for this observation? Could mild hypertension possibly be adaptive in the context of some other abnormality in pregnancy?

The view that hypertension might be adaptive is not new. Traube is said to have suggested that hypertension might be a homeostatic response to impaired renal excretory function as early as 1871.8 In this paper, we focus on ‘primary’ hypertension and ask if it could possibly be adaptive. This question follows from our belief that the circulatory system is a complex adaptive system that enables the blood flow demands of various organs of the body to be met. We too suspect that hypertension might be adaptive but in a different sense as detailed below.

**WHAT IS THE ‘GOAL’ OF SHORT-TERM AND LONG-TERM REGULATION OF CARDIOVASCULAR FUNCTION?**

Osborn et al. 9 have hypothesized that there exists a set point based on a MAP sensor in the brain determining the long-term level of MAP, independent of the arterial baroreflex arc. However, an apparently normal BP does not guarantee adequate tissue perfusion. For instance, in cerebral syncope, consciousness is lost despite an apparently normal BP because cerebral vascular resistance is paradoxically elevated although transiently. 10
Functional deficits in entities like stroke, myocardial infarction, are ultimately due to irrevocable disturbances in blood flow to part of the brain and heart respectively. Thus, it appears that cardiovascular regulatory mechanisms are eventually geared toward maintaining tissue blood flows commensurate with their metabolic demands, a function synergistic with other control mechanisms that enable optimal functioning of all organ systems of the body at all times and thereby maintenance of homeostasis. As tissue blood flow equals mean arterial pressure (MAP) divided by local vascular resistance, regulation of arterial BP is potentially one means of regulating tissue blood flow. It is acknowledged that the central nervous system (CNS) ischemic pressor response serves to eventually maintain cerebral blood flow. Indeed, recently Paton et al. have proposed that a physiologic Cushing’s mechanism triggered by a sensor of cerebral blood flow might play an important role in determining the long-term level of BP, and suggest that hypertension could be a homeostatic response to a primary increase in cerebrovascular resistance.

We believe that there exists a supply-demand relationship between the circulatory system (the supplier) and organs including the brain, heart, kidneys, other viscera, and skeletal muscle (all being consumers), which operates throughout life. In this scheme of thinking, all tissues (consumers) would have to maintain their respective demands for flow so that they may carry out their functions effectively, and also have the ability to autoregulate their flows commensurate with metabolic demand by varying local vascular resistance. The term ‘autoregulation’ here encompasses two possible responses at the level of each tissue: autoregulatory vasodilation in response to increased demand for flow; and
autoregulatory vasoconstriction in response to inappropriate overperfusion brought about by surges in BP. The notion that the CNS is the central controller in this paradigm arises from the following facts: one, errors in the supply-demand relationship between any consumer and the supplier are conveyed to the CNS via afferent neural or humoral signals from that consumer; two, the CNS regulates the level of activity of consumers (organs) and it is able to restrain blood flows to all tissues through sympathetic vasoconstrictor commands.

Obviously, autoregulation of local vascular resistance coupled to tissue metabolism is a highly effective means to regulate tissue blood flow. For instance, blood flow to metabolically active skeletal muscle can increase as much as 30 fold during intense exercise and this is largely due to autoregulatory vasodilation in exercising skeletal muscle; on the other hand, MAP does not vary more than 3-fold even when we consider extreme physiologic conditions such as sleep or intense exercise. However, raising BP can potentially contribute to meeting blood flow demands of metabolically active tissue, although it is quantitatively much less important in comparison to autoregulatory vasodilation as a mechanism for augmenting tissue blood flows. For example, during exercise, a reflex originating from metabolically active skeletal muscle (called the muscle metaboreflex or exercise pressor reflex) is known to be partly responsible for the pressor response to exercise. Thus, increments in cardiac output, total peripheral resistance (TPR) and BP that are driven by an error signal (hypoxia, ischemia) from one or more organs should be viewed as homeostatic as long as the error signal persists. A related homeostatic function of MAP is that autoregulation of tissue blood flows is operative
only when MAP is held within certain limits; for example, in health, autoregulation of cerebral blood flow is operative only when MAP is held between 65 and 140 mm Hg. The notion of a supply-demand relationship as a core characteristic of cardiorespiratory regulation and the role of the CNS as a central controller within this paradigm is not new (for example, Ref. 17) and is supported by experimental studies (e.g., Refs. 18, 19) but this concept is often used to illustrate only short-term regulation of cardiovascular function. Fink proposed conceptualizing the circulatory system as a regulated free market economy as a means to approach understanding long-term regulation of BP. Recurrent sleep apnea causing intermittent hypoxemia, which potentially jeopardizes delivery of oxygen to tissues, has been shown to lead to chronic sympathoexcitation and hypertension. Cardiorespiratory fitness has been shown to be an independent predictor of future hypertension among initially asymptomatic and normotensive healthy individuals. In this study by Barlow et al., the incidence of hypertension at 5 years follow up was 65% lower in women with high cardiorespiratory fitness compared to women with low fitness after adjustment for several potential confounders, and a one metabolic equivalent increment in estimated maximal oxygen uptake was associated with a 19% reduction in risk of incident hypertension. These observations strongly support the use of a simple analytic framework, i.e., the notion of a supply-demand relationship between the circulatory system and other organs alluded to above, for exploring and understanding long-term regulation of cardiovascular function.

It follows that when there is a primary persistent defect in autoregulation of blood flow in
organs such as the kidneys, heart, brain or muscle, increments in BP will play an increasingly important role in meeting the flow requirements of the affected organs. It appears that the most the CNS can contribute in terms of compensating for an organ’s inability to augment its flows by vasodilation is to increase arterial BP.

**HYPOTHESIS: DEFECTS IN AUTOREGULATORY VASODILATION ARE AN ULTIMATE CAUSE OF HYPERTENSION**

Autoregulatory vasodilation is achieved primarily by the actions of products of tissue metabolism on the endothelium and smooth muscle of arterioles in that tissue. Interestingly, several factors that put an individual at risk of hypertension are independently associated with endothelial dysfunction, a phenotype characterized by defective autoregulatory vasodilation: cigarette smoking, dyslipidemia, obesity, insulin resistance. By endothelial dysfunction (sometimes referred to as ‘endothelial activation’) is meant endothelial function defective at least in its vasodilator capacity although such dysfunction in clinical states is typically additionally associated with a proinflammatory, proatherogenic, prothrombotic phenotype. The reader is referred to recent reviews on what constitutes endothelial dysfunction, how it is assessed, and the clinical implications of this phenotype.

In keeping with our understanding of cardiovascular regulation summarized above, we hypothesize that chronic endothelial dysfunction impairing autoregulatory vasodilation in tissues will lead to tissue hypoxia/ischemia and this will activate a ‘metaboreflex’ from affected tissues. This ‘metaboreflex’ would elicit increments in sympathetic outflow to
capacitance vessels, heart, resistance vessels and kidneys and consequently bring about a rise in cardiac output, and or a sustained rise in total peripheral resistance. The term ‘metaboreflex’ is used in this paper in a wider sense than traditionally to refer to afferent neural or humoral signals originating from any organ (not just skeletal muscle) in response to accumulation of products of metabolism or an unfulfilled demand for oxygen or energy substrates, evoking reflex neurohumoral adjustments that eventually serve to fulfill them.

First, all cells are able to meter their oxygen levels, energy charge and pH, and this is linked to modulation of hypoxia-inducible factors and a transcriptome mediating adaptive cellular responses. Second, there is evidence for the presence of metabosensitive afferent neurons in the heart, kidneys, and skeletal muscle. The stimulus for the CNS ischemic pressor response is neuronal ischemia; thus, according to our view, it is a ‘metaboreflex’. As for feedback signals from kidneys, the traditional view is that autoregulation of renal blood flow and glomerular filtration rate occur independent of renal metabolic demand; however, the vulnerability of renal medulla to hypoxic damage in the context of a decrease in renal perfusion is well known and thus it is possible that ischemic renal medulla might be the source of a ‘metaboreflex’ traveling via the renal afferents and activating efferent sympathetic outflow. Indeed, there is evidence that renal deafferentation significantly reduces BP but the contribution of sensory receptors sensitive to changes in renal cellular metabolism in these conditions remains to be elucidated.
Several reports describe the role of the muscle metaboreflex in the acute cardiovascular responses to exercise or other stressors. However, now it is clear that primary sensory neurons activated by products of tissue metabolism and eliciting reflex sympathoexcitation are present in the heart, kidneys, and other viscera as well. Lactic acid liberated from ischemic mesentery has been shown to activate afferents and elicit reflex sympathoexcitation. Transient receptor potential Vanilloid (TRPV) channel mediated reflex sympathoexcitation has been shown to be augmented in rats with vascular insufficiency induced by femoral artery ligation for 24 hours. Pan and Chen have demonstrated that the capsaicin sensitive vanilloid receptor-1 is essential for myocardial ischemia induced activation of cardiac sympathetic afferent neurons and the ensuing pressor response. Recently, Wang et al. have shown that deletion of the TRPV1 gene aggravates hypertension induced renal damage in rats with deoxycorticosterone-induced hypertension. According to our hypothesis, renal cellular ischemia would be expected to activate a metaboreflex and consequently an increase in sympathetic nerve activity and BP. If TRPV1 receptors simply transduced renal cellular ischemia, then, the absence of TRPV1 in renal sensory neurons would be expected to result in little change in efferent sympathetic nerve activity and consequently little change in renal excretion of sodium and water. This appears not to be the case; in fact sodium excretion caused by salt loading has been shown to be reduced following renal sensory nerve degeneration induced by neonatal capsaicin treatment. This indicates that TRPV1 channels mediated an antihypertensive effect in the study by Wang et al. It is important to note that the TRPV channel, while being activated by products of tissue metabolism including adenosine, low pH, is a polymodal receptor transducing other stimuli such as
temperature and mechanical stimuli. 52

In a study aimed at investigating the link between endothelial function and the muscle metaboreflex, Guazzi et al. 54 report improvement in endothelial function with cardioversion to translate to improvement in ventilatory efficiency in hypertensives with atrial fibrillation. However, a fundamental question for future investigations is how much the muscle metaboreflex or a metaboreflex from other tissues including the brain, heart and the kidneys contributes to resting MSNA and SNA in other vascular beds in health as well as in pathophysiologic states such as primary hypertension and heart failure, conditions in which baseline MSNA is typically elevated.

Our hypothesis is compatible with the notion expressed by Guyton and colleagues 55 that impairment of natriuretic responses is a crucial determinant of the long-term level of BP. This is because endothelial dysfunction is usually a systemic abnormality although the severity of dysfunction might vary in different vascular beds. 31 Renal endothelial dysfunction impairing autoregulatory vasodilation in the kidneys would eventually be expected to shift the relationship between MAP and natriuresis to higher arterial pressures.

The concept that endothelial dysfunction defective in its vasodilator capacity is a cause of hypertension is not new. Our intention here is rather to suggest that metaboreflex mediated increments in sympathetic outflow consequent to endothelial dysfunction are essentially homeostatic since they would be initiated by persistent error signals from
ischemic tissues and contribute to eventually normalizing tissue blood flows, though at the expense of chronically elevated BP (summarized in Fig. 1). This is not to deny that hypertension itself constitutes a risk factor for progression of endothelial dysfunction. It is worth noting that the hypothesis proposed above pertains largely to the initiation of hypertension. High TPR in the established phase of hypertension may be due to structural autoregulatory changes in the resistance vessels that amplify the rise in arterial pressure as described by Folkow 56 and Korner 57 and possibly the persistence of metaboreflex mediated sympathoexcitation relative to that in the normotensive state. Furthermore, hypertension aggravates endothelial dysfunction 58-59 establishing a vicious cycle that leads to further elevation of BP; however, breaking a vicious cycle such as by merely lowering BP with antihypertensive drugs is in itself inadequate.

Age is the single most important factor associated with hypertension 2, and aging is associated with endothelial dysfunction 60 as well as increased sympathetic activity. There is evidence that endothelial dysfunction antedates the development of hypertension 61 or is present in individuals at significant risk of future hypertension 62-63. In support of the concept of developmental origins of cardiovascular disease, dietary protein restriction in pregnant rats has been shown to lead to endothelial dysfunction and vascular remodeling in the offspring. 64 Obesity, a leading risk factor that independently predicts future hypertension, 65-66 is associated with endothelial dysfunction 27, 67 and elevated sympathetic activity. 68 Endothelial activation and dysfunction is a fundamental event in the pathogenesis of atherosclerosis. 30-34 It has been suggested that microalbuminuria, a predictor of incident hypertension, may reflect systemic endothelial dysfunction. 69 In a
prospective study of 225 adults aged 35-54 years with never treated hypertension, Perticone et al. found that individuals with the lowest forearm blood flow increments to intra-arterial acetylcholine were twice more likely to develop cardiac or cerebrovascular events at 31 months follow up even after adjustments for 24 hour ambulatory BP.

Uteroplacental hypoperfusion, considered the initiating event in pregnancy-induced hypertension, is known to lead to dysfunction in the maternal vascular endothelium. It is possible that uteroplacental ischemia is also the precursor of the exaggerated increase in sympathetic nerve activity in pregnancy-induced hypertension, and the rise in BP is only more likely to normalize uteroplacental perfusion. In that sense, one could argue that the sympathoexcitation in pregnancy-induced hypertension is homeostatic. This may be one physiological mechanism that explains why Abalos et al. found little benefit in lowering BP in pregnant women with mild to moderate hypertension.

**TESTING THIS HYPOTHESIS:**

An experimental approach to testing this hypothesis would be to induce extensive endothelial dysfunction and follow metaboreflex mediated increase in SNA or surrogates of it to the heart, blood vessels and kidneys over a reasonable time period. In another group of animals with endothelial dysfunction, if we were to interfere with the metaboreflex-mediated rise in sympathetic efferent activity, this would be expected to accelerate the development of circulatory failure, organ dysfunction and eventually death.
If this hypothesis were correct, we could claim that hypertension is essentially adaptive in this context. Since natural selection would have favored genotypes that are associated with reproductive fitness, the long-term consequences of hypertension i.e., the increased risk for stroke, myocardial infarction, and renal failure, which typically occur much later in life, could be viewed as a price paid for this adaptation. Indeed, hypertension can be asymptomatic for years to decades before it results in a clinically significant complication.

Targeted disruption of the endothelial nitric oxide synthase provides a useful animal model of endothelial dysfunction. eNOS null mice are characterized by hypertension, enhanced BP variability, and increased neointimal response to vascular injury. However, it is important to note that expression of eNOS is not limited to vascular endothelial cells; for example, it has been found to be expressed in cardiomyocytes, as well as in myenteric neurons and interstitial cells of Cajal. This issue may be addressed by using technology that enables generation of tissue specific inactivation of a gene of interest; i.e., a mouse model with endothelial cell specific inactivation of the endothelial nitric oxide synthase gene would be ideal. An alternative approach would be to strip substantial segments of endothelium from strategic locations such as aorta, renal arteries, carotid arteries or coronary arteries depending on the vascular bed we wish to investigate. For example, stripping the endothelium from coronary arteries would be expected to activate a metaboreflex from ischemic myocardium. Examining the effects of desensitization of primary afferent neurons in the heart with resiniferatoxin on baseline SNA might help elucidate the role of this coronary metaboreflex (also called
cardiac sympathetic afferent reflex) in this model. However, experimental induction of endothelial dysfunction in one vascular bed such as by stripping of endothelium might not necessarily simulate the pattern of endothelial dysfunction observed in clinical states. This is because while the coronary arteries and carotid arteries are more vulnerable to frank atherosclerosis, endothelial dysfunction is typically a systemic abnormality as evidenced, for example, by coexistence of impaired flow mediated dilator responses in the forearm and the coronary microcirculation. 34, 76

Given that primary hypertension typically evolves over a very long time scale, the question of how long one must follow changes in SNA after induction of endothelial dysfunction in an experimental animal model is difficult to answer but one would expect the extent of endothelial dysfunction and the average metabolic demand for energy substrates and oxygen during the period of investigation to be the two most important factors. Finally, because sympathetic outflow to various vascular beds may be differentially regulated, 77 temporal changes in sympathetic outflow to various vascular beds should be expected. There is strong and consistent evidence that differential activation of the sympathetic nervous system can occur in conditions of chronic energy imbalance. For example, Esler and colleagues 78 have reviewed the evidence that positive energy balance in humans and animals produces a relatively selective activation of the renal sympathetic nerves.

Two potential implications, if this hypothesis is verified, are as follows: first and most obviously, BP lowering without primary attention to the underlying cause of hypertension
is potentially dangerous; second is the issue of whether it matters which drugs are used to lower BP or whether it is BP lowering alone that matters. Indeed, if endothelial dysfunction were proven to be a cause of hypertension and the sympathoexcitation occurring therein proven to be essentially adaptive, therapy would have to focus on improving endothelial function rather than merely lowering BP. Some antihypertensive drugs like ACE inhibitors improve endothelial function while beta-blockers like atenolol don’t. 35 This might explain differences in clinical outcomes with different antihypertensive drugs that are independent of BP lowering. For example, in a small study of subjects with essential hypertension treated with a combination of losartan and hydrochlorothiazide, Fu et al. 79 observed a persistent increase in muscle sympathetic nerve activity (MSNA) after 3 months therapy although there was a substantial lowering of resting BP. This observation suggests, at the least, that the arterial baroreflex does not reset to a lower BP level or BP lowering therapy did not address the actual cause of sympathoexcitation. What then is/are the actual mechanism(s) of sympathoexcitation in these subjects? Fu et al. did not examine endothelial function in this study but since endothelial dysfunction is invariably present in hypertensives, one possibility is that substantial lowering of BP and consequently blood flows to tissues could have activated a metaboreflex from underperfused tissues thereby driving sympathetic activity. Aortic diastolic pressure reduction in hypertensive dogs to levels well tolerated in normotensive dogs, has been shown to reduce coronary blood flow, the ratio of endocardial-to-epicardial flows and induce systolic dysfunction. 80 On the other hand, azelnidipine, a long acting calcium channel blocker, has been shown to improve expression of endothelial nitric oxide synthase in the brain, heart and aorta, and lower SNA as well as
BP in stroke-prone hypertensive rats. \(^8\)

In contrast to the hypothesis presented in this paper, Weder \(^8\) suggests that natural selection must have duplicated genes required for hypertension in response to some other pressure to optimize fitness in ancestral environments, and that hypertension is now an undesirable pleiotropic effect of this preserved genotype. There is evidence supporting this point of view: the hot, wet and salt scarce climate of Africa necessitated the duplication of genes that preserve salt and water. This would explain why Americans of African origin develop hypertension faster, more frequently, as well as severe hypertension. This is supported by a rising frequency outside of Africa of functional alleles (e.g., in the angiotensinogen gene) that reduce salt and water avidity. \(^8\)

Hypertension accompanying obesity has also been viewed as an undesirable effect of sympathetic activation primarily aimed at regulating body weight. \(^8\)

**SUMMARY AND CONCLUSION:**

There is evidence that single unit MSNA with vasoconstrictor properties is raised in primary hypertension. \(^8\) While there is considerable overlap in MSNA between normotensives and hypertensives, \(^8\) a positive correlation between plasma levels of nitrates and MSNA has been demonstrated in normotensives thereby raising the possibility that there is a balance between sympathetic activity and vasodilating mechanisms. \(^8\) The role of the arterial baroreflex, the renal renin-angiotensin system, and the arterial chemoreflex in the long-term regulation of SNA and BP has been the subject of intense investigation and debate (reviewed in Refs. 21, 22, 89 and references therein).
In this paper, we have presented the hypothesis that, in the context of a primary defect in autoregulatory vasodilation of tissue blood flows caused by chronic endothelial dysfunction, a metaboreflex from ischemic tissues would contribute to the increase in BP by activating the sympathetic nervous system, and that this is essentially a homeostatic response. The contribution of this ‘metaboreflex’ to the long-term level of MAP merits investigation. Hypertension is a heterogeneous entity; thus we wish to clarify that our intention is not to suggest a unifying hypothesis for development of hypertension. However, even if it turns out that endothelial dysfunction is the ultimate cause of only about 10% of all clinical hypertension, the overall impact of a therapeutic approach focused on the actual cause would be considerable given the enormous global public health burden attributable to hypertension.

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**Figure 1** – A hypothetical link between chronic endothelial dysfunction, ‘metaboreflex’ from ischemic tissues, efferent sympathetic nerve activity and the long-term level of blood pressure.

Genetic and environmental risk factors

- Chronic endothelial dysfunction defective in its vasodilatory capacity
  - **Chronic ischemia of affected tissues (heart, brain)**
  - **Chronic activation of metabosensitive neural signals from ischemic tissues**
  - **Reflex increase in efferent sympathetic nerve activity**

- Renal ischemia due to defects in autoregulation of renal blood flow
  - **Activation of metabosensitive afferent neurons in kidney**

- Vasoconstriction due to deficiency of vasodilators
  - **Activation of the renin-angiotensin-aldosterone system**
  - **NaCl and water retention**

- Rise in total peripheral resistance, cardiac output
  - Rise in total peripheral resistance

- Amplification and maintenance of hypertension by structural adaptations in blood vessels and heart

*Hypothetical events are italicized.*