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# Central Nervous System Neuroplasticity and the Sensitization of Hypertension

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## Abstract

The causes of essential hypertension remain an enigma. Interactions between genetic and external factors are generally recognized to act as aetiological mechanisms that trigger the pathogenesis of high blood pressure. However, the questions of what genes and factors are involved, and when and where such interactions occur, remain unresolved. Emerging evidence indicates that the hypertensive response to pressor stimuli, like many other physiological and behavioural adaptations, can become sensitized to particular stimuli. Studies in animal models show that, similarly to other response systems controlled by the brain, hypertensive response sensitization (HTRS) is mediated by neuroplasticity. The brain circuitry involved in HTRS controls the sympathetic nervous system. This Review outlines evidence supporting the phenomena of HTRS and describes the range of physiological and psychosocial stressors that can produce a sensitized hypertensive state. Also discussed are the cellular and molecular changes in the brain neural network controlling sympathetic tone involved in long-term storage of information relating to stressors, which could serve to maintain a sensitized state. Finally, this Review concludes with a discussion of why a sensitized hypertensive response might previously have been beneficial and increased biological fitness under some environmental conditions, and why today it has become a health-related liability.

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Both authors contributed to discussions of the article content, researched data for the article, and drafted and edited the manuscript before submission.

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## Introduction

Environmental and physiological challenges encountered throughout one's lifetime can induce long-lasting adaptations in physiological and behavioural systems. Many times the consequence of such experientially induced adaptations is increased biological fitness. However, in some cases, antecedent life events can act as strong aetiological factors that set the stage for subsequent challenges (or stressors) to trigger the onset of disease.

Among the important roles of the central nervous system (CNS) is the control of physiological and behavioural systems that maintain homeostasis as well as manage other complex functions, such as the integration of sensory and motor information and reproduction. Complex neural networks have been identified that control such functional systems. These networks are composed of many neuronal cell groups (nuclei) connected to one another by nerve pathways (tracts). Neural networks integrate and process incoming (afferent) information, which results in outgoing (efferent) signals that determine whether and to what extent particular behavioural, neural, immune or endocrine responses are elicited. Such networks are involved in both the short-term and long-term control of physiological and behavioural functions. Reflexes that are innate, hardwired and genetically determined mediate short-term responses to a particular stimulus. By contrast, long-term modifications can be introduced into neural networks to alter the control of functional systems. Neural networks also encode and store information about past events for later retrieval. This 'memory' property of adaptive neural control of effector systems involves neuroplasticity and enables new responses to be acquired or the magnitude of responses to a previously encountered stimulus to be adjusted in the face of new challenges or environmental changes.

One of the simplest forms of neurally mediated adaptation is response sensitization . The neural networks and cellular and molecular mechanisms involved in response sensitization have been studied in many functional systems, including pain, motivation, drug addiction, respiratory control, stress, salt appetite, and exercise. However, the hypertensive response to pressor stimuli has only recently[1,2] been recognized as a mechanism that can become sensitized, and the neural mechanisms that mediate hypertensive response sensitization (HTRS) are, therefore, being actively investigated. Information from such studies provides a fresh understanding of what is likely to be an important causal mechanism of some forms of essential hypertension

In this Review, we describe insights into the mechanisms underlying HTRS derived from investigations into the conditions that induce this phenomenon. We also discuss how an induction-delay-expression (IND-DEL-EXP) experimental paradigm can be applied to investigate the neuroplasticity underlying HTRS and how activity-driven CNS neuroplasticity induced either in the perinatal period or in adulthood can maintain the propensity for increased sensitivity of the hypertensive response to pressor stimuli, perhaps even over the course of a lifetime. These topics will be introduced by discussing the nature of essential hypertension and the probable role of the sympathetic nervous system (SNS) in its pathogenesis. Also described are the types of stimuli and conditions that can activate and

modify central neural networks, thereby changing the responsiveness of the SNS and altering the long-term regulation of blood pressure.

## Physiological and psychosocial stress

For over 100 years, the SNS has been recognized as a key adaptive system that corrects factors that challenge homeostasis[3–5]. Actual dyshomeostasis or threats that might disrupt the stability of the internal environment activate the SNS. The latency of sympathetic activation (that is, the time interval between stimulus and response) under such circumstances is nearly instantaneous, and its effects are more rapid than those of other systems (such as endocrine, immune or behavioural responses) that are mobilized subsequently to restore dislocations from homeostatic norms.

The stimuli or conditions that increase sympathetic activity can vary over a range of intensities and produce graded degrees of regional sympathetic activation. For example, an external threat evokes strong behavioural (aggression or running away) and cardiovascular (a haemodynamic pattern characterized by increased cardiac output, increased skeletal muscle blood flow, and decreased flow to renal and mesenteric vascular beds) changes. This has been dubbed the ‘fight - flight’ response.

The term stress was used to describe both the sympathetic and the behavioural responses to noxious or threatening challenges[3–5]. Later research showed that behavioural and cardiovascular components of the fight - flight response could be elicited by stimulating the hypothalamus[6,7], amygdala[8], dorsal tegmentum and central grey[9]. In turn, these studies were followed by elucidation of the role of the hypothalamo–pituitary–adrenal axis in response to stressors, and the general adaptation syndrome[10–12]

A stressful stimulus (or stressor) can be characterized as physiological or psychosocial. Physiological stressors (also known as systemic, homeostatic or interoceptive stressors[13–15]) are challenges that result from an immediate disruption in homeostasis, such as hypoxia, hypovolaemia, extracellular hypertonicity or hypoglycaemia. By contrast, psychosocial stressors (also known as psychological, processive, neurogenic, mental or exteroceptive stressors[13–15]) do not immediately disrupt homeostasis but are perceived as posing a threat to an individual’s physical or psychological integrity. Examples of psychosocial stressors are restraint, conditioned fear and psychosocial defeat. Psychosocial stressors include both non-conditioned, prepotent stimuli, such as the sight, sound or odour of a predator, fear of heights or fear of snakes, and conditioned stimuli that, despite being initially neutral or innocuous, have become linked to aversive responses through associative learning (also termed classical or Pavlovian conditioning). Psychosocial stressors engage sensory receptors and their afferent pathways (related to sight, hearing, smell, touch and taste) and involve the limbic system (including the amygdala, hippocampus and medial prefrontal cortex) in information processing. Psychosocial stressors that elicit sustained or repeated SNS activation are hypothesized to be important causes of essential hypertension, discussed below[16–19].

## Essential hypertension

High blood pressure or hypertension is the leading risk factor for disability and death worldwide[20,21]. Hypertension increases the likelihood of many major disorders, including heart and kidney disease, stroke, dementia and retinopathy. In 2015 the number of adults with hypertension worldwide was estimated to be 1.13 billion[22]. A cross-sectional study of individuals aged 35–70 years from 17 countries estimated that 40.8% were hypertensive[23]. New guidelines[24] announced in 2017 will further increase the number of individuals considered to have hypertension, as the new threshold values for systolic and diastolic blood pressure are lower than those used previously for diagnosis of hypertension[25].

Patients in whom hypertension can be attributed to an underlying medical condition or medication are diagnosed as having secondary hypertension. However, these individuals account for 10% or less of the total hypertensive population. For the majority of hypertensive adults, the aetiology of the disease is unknown and they are consequently diagnosed as having primary (or essential) hypertension. Essential hypertension is recognized to be a multifactorial disorder involving multiple genes and environmental influences[26,27]. Almost certainly, several subtypes of essential hypertension will be identified, with different aetiologies and courses of development resulting from the interactions of multiple genetic and environmental factors.

### The role of tissue perfusion factors

Increased systemic vascular resistance is the proximal cause and hallmark of established essential hypertension[28,29]. Early studies of the mechanisms responsible for cardiovascular homeostasis identified multiple interacting factors that control tissue perfusion, including chemical and neuromodulatory agents, and factors that control cardiac and vascular reactivity, blood volume, blood pressure and blood viscosity[30]. In recognition of the fact that blood pressure is a mechanism for controlling tissue perfusion, the mosaic theory of arterial hypertension proposed that these interacting factors were also likely to contribute to the pathogenesis of hypertension[30,31]. This theory led to the inevitable question of whether a fundamental fault in these systems causes essential hypertension[32] — that is, whether a single cause of essential hypertension could be identified.

One approach to evaluate the relative contribution of various factors involved in the control of tissue perfusion and blood pressure regulation was to apply computer modeling with parallel animal experiments to test the relative contributions of various candidate factors[33–35]. These studies showed that normal kidneys have an infinite capacity to normalize blood pressure in response to changes in salt and water intake and excretion. By contrast, impairment in renal function reduces sodium and water excretion, which leads to increased extracellular volume and, in turn, to increases in blood volume and cardiac output. One route to increased systemic vascular resistance is thought to be mediated by the phenomenon of total body autoregulation, in which vasoconstriction is triggered by over-perfusion of tissues[36].

### The role of SNS overactivity

The role of the CNS in blood pressure regulation was initially thought to be limited to the baroreflexes and chemoreflexes. Such reflexes were considered to be involved only in short-term regulation of blood pressure; they were considered to have no role in the long-term control of blood pressure because these reflexes adapt to chronically high or low blood pressures[37,38]. Consequently, the role of the CNS in the regulation of blood pressure and in the pathogenesis of essential hypertension was largely disregarded.

However, overactivity of the SNS is now considered a major cause of essential hypertension[39–42]. Studies measuring sympathetic nerve traffic and norepinephrine spillover have provided direct evidence for sympathetic activation of the skeletal muscle, heart and kidney in the early and established stages of essential hypertension[43,44]. As essential hypertension progresses, this increased sympathetic drive contributes to end-organ damage[45]. Some patients with elevated SNS tone respond to treatment with sympatholytic drugs by a decrease in blood pressure. At least 50% of patients with primary hypertension are estimated to have this neurogenic form of essential hypertension[46]. Among the most important issues to be addressed for understanding the causes and course of essential hypertension is identification of the mechanisms responsible for inducing and initiating the early increase in SNS activity and for sustaining the potential for increased SNS drive. If the SNS does indeed play an important part in the pathogenesis of essential hypertension, the next questions that arise are what factors or mechanisms lead to this excess SNS activation, and how do they result in long-term increased systemic vascular resistance (FIG. 1).

## The central sympathetic nervous system

The SNS and the parasympathetic nervous system are two branches of the autonomic nervous system (ANS). Both sympathetic and parasympathetic arms influence activity of the heart, and the sympathetic component acts on the vasculature. Portions of the ANS are located in both the periphery (peripheral ganglia and nerves) and CNS (brain and spinal cord). Insight into how the SNS contributes to the long-term control of blood pressure necessitates some familiarity with its central organization.

The CNS portion of the ANS is a neural network that receives and integrates inputs from somatic and visceral sensory systems. The consequence of this central processing is the generation of a pattern of autonomic and endocrine system responses that determine blood pressure on a moment-by-moment basis. The number of brain nuclei involved in the control of sympathetic tone and blood pressure is large, and their connections and functional interactions are complex[47,48]. It is likely that multiple sites within the neural network controlling SNS activity store information about prior SNS activations resulting from physiological and psychosocial stressors.

The neural systems implicated in sympathetic responses to physiological and psychosocial stressors share some common elements, but they also have some different components. Probably the best-characterized central circuitry controlling SNS tone is that related to systemic stressors affecting the control of blood pressure and body fluid homeostasis (reviewed elsewhere[47–50]). The brain receives information about blood pressure and

extracellular fluid status through two different modes of body–brain communication: afferent neural input from the vasculature, and humoral input acting directly on target tissues in the brain. Mechanoreceptors in the venous and arterial vasculature sense changes in blood pressure and blood volume, causing a change in afferent nerve signaling to the nucleus tractus solitarius (NTS), which triggers corrective reflexes. Humoral signals, by contrast, act on two forebrain regions that lack a blood-brain barrier: the subfornical organ (SFO), and the organum vasculosum of the lamina terminalis (OVLT)[51]. The SFO contains receptors for angiotensin-II (ANG II) and the OVLT includes osmoreceptors that detect extracellular solute concentrations (mainly $Na^+$). The SFO and OVLT, along with the median preoptic nucleus (MnPO), process information relevant to the status of blood volume, pressure and extracellular fluid osmolality[52]. (FIG. 2).

Hindbrain structures (the NTS and parabrachial nucleus (PBN) are connected to rostrally located structures in the hypothalamus, amygdala and along the lamina terminalis; reviewed elsewhere[47–49,53]). The hypothalamic paraventricular nucleus (PVN) is a key area in the hypothalamus that receives both ascending input from the hindbrain and descending input from the SFO, OVLT and MnPO. The PVN, therefore, functions as a key integrative node for processing information important for maintaining body fluid and cardiovascular homeostasis. Sympathetic premotor neurons projecting from the PVN innervate the intermediolateral cell column (IML) of the spinal cord, either directly or indirectly via the rostral ventrolateral medulla (RVLM). The IML contains the preganglionic cell bodies of sympathetic axons leaving the CNS, which act as the final common path for the SNS (FIG. 2).

In comparison to the neural pathways mediating responses to challenges associated with altered fluid balance and blood pressure, the network that controls SNS activity associated with psychosocial stressors is not very well defined. However, some major components have been identified, mainly by functional mapping [49,54–56]. The amygdala is a key structure in mediating responses to psychosocial stressors. The short neural path from exteroceptive sensory receptors to the amygdala enables rapid activation of responses to environmental stressors that signal danger[57]. The amygdala also receives inputs from the medial prefrontal cortex and hippocampus, which are involved in memories of previously learned associations with conditioned stimuli[54]. In the diencephalon, the lateral hypothalamus /perifornical area[55–58] and the dorsomedial hypothalamus have both been implicated in the cardiovascular components of the fight or flight response[53,59,60]. An output pathway projects from the dorsomedial hypothalamus to the rostral ventromedial medulla, and contains sympathetic premotor neurons that project to the IML[49,53].

## The renin–angiotensin–aldosterone system

The discovery of the enzyme renin and its substrate, angiotensinogen[61], precipitated the elucidation of a major pressor system involving renin, angiotensinogen, angiotensin-I (ANG I), angiotensin-converting enzyme (ACE) and ANG II (reviewed elsewhere[62]). ANG II exerts its actions by binding to the type 1 and type 2 ANG II receptors (named AT1 and AT2, respectively). Because ANG II is a major determinant of circulating aldosterone levels,

and ANG II and aldosterone have many common functions, this system is often referred to as the renin–angiotensin–aldosterone system (RAAS).

Several other elements of the RAAS have since been discovered. A homologue of ACE, ACE2, removes a carboxy-terminal phenylalanine from ANG II to produce a heptapeptide, $ANG_{1–7}$, which binds to the Mas-related G-protein coupled receptor MRG (also known as MASR). $ANG_{1–7}$, ACE2 and MASR are considered to be components of a counter-regulatory (that is, antihypertensive) arm of the RAAS[62–64]. ANG II itself could also have both hypertensive and antihypertensive actions, as the effects of ANG II binding to AT2 oppose those produced by its binding to AT1[62,63].

In the early 1970s, so-called brain renin or isorenin (a renin-like substance discovered in the brain, probably cathepsin D) was thought to be the first brain RAAS component[65,66]. It is now recognized that most components of the RAAS are synthesized in the CNS as well as at many sites in the body, including the vascular wall, heart, adipose tissue, haemopoietic bone marrow, lungs, and the gastrointestinal tract[62,63]. Although some controversy remains, work by many contributors has resulted in a general consensus that essentially all RAAS components are generated *de novo* within the mammalian CNS and that the weight of the evidence favours the existence of a brain RAAS[67–71].

It is important to understand how the peripheral RAAS is related to the brain RAAS. Many early studies investigating communication between the peripheral and brain RAASs led to the proposal that circulating ANG II acts on the SFO in the mode of a circulating hormone to activate ANG II-containing efferent neurons that use ANG II as a neurotransmitter or neuromodulator [72–74]. Substantial evidence continues to support this concept of humoral–neural coupling between the circulating and brain RAASs (reviewed elsewhere[75]). In the brain, ANG II is likely to function as an excitatory neuromodulator that acts in concert with excitatory neurotransmitters (such as glutamate) at synapses in the descending pathway between the SFO and IML to increase SNS activity[75] (FIG. 2) and thereby induce activity-driven neuroplasticity.

## Microglia and pro-inflammatory cytokines

Both neurons and brain glial cells participate in the orchestration of cardiovascular and metabolic functions[76,77]. The brain has its own innate immune system; microglia are macrophages that migrate into the brain early in development and become its resident immune cells. Both systemic and brain components of the immune system use cytokines for autocrine, paracrine and endocrine (extracellular) signaling involved in immunomodulation. Levels of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β, are increased in cardiovascular disease states, and extensive evidence indicates that these cytokines contribute to SNS activation in heart failure and hypertension[78,79].

Activated brain microglia release pro-inflammatory cytokines and upregulate their production of extracellular and intracellular reactive oxygen species[80–82]. Both spontaneously hypertensive rats and animals with ANG II-induced hypertension show

microglial activation within the PVN, associated with increased levels of pro-inflammatory cytokines[80–82] or targeted depletion of activated microglia within the PVN attenuates ANG II-induced hypertension and decreases both pro-inflammatory cytokine levels within the PVN and cardiac hypertrophy[81,82]. These results indicate that ANG II-induced microglial activation and the subsequent release of pro-inflammatory cytokines contribute to the development of hypertension. Of note, ANG II itself can activate microglia and stimulate the release of pro-inflammatory cytokines[82,83].

Pro-inflammatory cytokines released in the periphery and in the brain as a consequence of RAAS activation can also upregulate AT1. Blood-borne pro-inflammatory cytokines can increase SNS activity and elicit a pressor response by acting on the SFO to increase brain RAAS activity and inflammation[84–86]. This finding suggests that the SFO-mediated sympathoexcitatory response to pro-inflammatory cytokines depends on having an ambient level of activity of both the brain RAAS and pro-inflammatory cytokines[84–86].

## Plasticity in neural networks

Late in the 19th century, the idea that the relationship between cells of the nervous system could be modified and that life experiences could produce such changes provided the first structural basis for memory (reviewed in [87]). Half a century later, a functional hypothesis accounting for the storage of information involving the synapse was proposed[88]. According to this hypothesis, the close temporal contiguity of activation of a presynaptic neuron immediately followed by firing of a postsynaptic neuron strengthened the connection between the two cells.

Further support for this functional hypothesis was generated by experiments demonstrating that the strength of synapses could be modified by delivering high-frequency electrical stimulation to a pathway projecting onto hippocampal granule cells[89]. The stimulation induced facilitation of extracellular field potentials in the dentate gyrus of the hippocampus that lasted for a sustained duration, suggesting that the phenomenon was akin to memory. This enhanced response, known as long-term potentiation (LTP), can be induced at many other sites in the nervous system[90,91], including the sympathetic ganglia[92,93].

At the time LTP was discovered, investigators in the field of memory and learning classified learning as either associative or non-associative. Two forms of associative learning are classical or Pavlovian conditioning and instrumental conditioning (also known as operant conditioning). In both forms of associative learning, a neutral stimulus becomes associated with a response (or with another stimulus) as a result of the subject undergoing a conditioning procedure. Non-associative learning does not require a neutral stimulus; however, repeated presentations of a stimulus produce a change in the magnitude of an elicited response. A decrease in response amplitude after repeated stimulation is termed habituation, whereas an increase in response amplitude is termed sensitization. Habituation occurs when a stimulus provides little relevant information — particularly when it proves to be non-aversive and non-threatening. Response sensitization occurs when a stimulus is injurious or threatening, and activates defensive physiological and behavioural responses.

The study of response sensitization in mammals and lower species led to the discovery of many fundamental cellular and molecular mechanisms that are important for the formation and retention of memories[94,95]. Neural mechanisms responsible for sensitization have been investigated in many functional systems, including pain[96–98], cravings for drugs of abuse[99–102] or salt[103,104], baroreceptor and chemoreceptor-reflexes[105,106], reflex motor responses[107], intermittent hypoxia[108,109], respiration[110,111], stress[112,113] and exercise[114,115]. Progress in investigating the role and mechanisms of neuroplasticity in sensitization of many of these CNS-supervised functional systems has been rapid because the neural pathways controlling these responses have been defined. The neuroanatomy of the brain network controlling SNS activity and blood pressure has also been characterized. However, only recently have we recognized that HTRS exists and is mediated by maintained neuroplasticity[1,116].

The evidence supporting the existence of a modifiable CNS-network-embedded controller of SNS activity and blood pressure is discussed in the next section. This CNS controller of sympathetic tone is adaptive and can alter long-term regulation of blood pressure as a result of prior experience[117,118]. In other words, an altered cardiovascular response is learned as a result of the presence of an antecedent stimulus. This sensitized capacity to increase SNS activity in response to physiological and psychosocial challenges provides a working hypothesis to explain how exposure to stressors earlier in life can, through vascular and renal mediators, lead to increased systemic vascular resistance and high blood pressure at a later time (FIG. 1).

## Hypertensive response sensitization

### IND-DEL-EXP experiments

Our research group has investigated sensitization of the hypertensive response using an IND-DEL-EXP experimental paradigm (BOX 1)[1]. In in an initial experiment a very low, non-pressor dose of ANG II was administered during the induction phase. After a 1-week delay period, animals exposed to the non-pressor dose of ANG II during the induction phase show a significantly enhanced hypertensive response during the expression phase, compared with control animals that received vehicle during the induction phase (BOX 1). A follow-up experiment demonstrated that the HTRS-inducing effects of ANG II were mediated by the CNS. Intracerebroventricular administration of very low (non-pressor) doses of ANG II during the induction phase had no sustained effect on blood pressure during the induction and delay phases yet still induced HTRS[1] . Additional evidence implicating the CNS in HTRS was provided by experiments showing that intracerebroventricular administration of irbesartan (an AT1 antagonist) along with subcutaneous low-dose ANG II in the induction phase prevented HTRS[1].

By employing the IND-DEL-EXP experimental design, it was possible to provide the first unambiguous demonstration that the hypertensive response can be sensitized[1]. The power of the IND-DEL-EXP method is that it disambiguates induction of a sensitized response from expression of sensitization. Most procedures used to induce hypertension conflate the time and processes involved in inducing sensitization with the period of expression of the hypertensive response. A retrospective view of the literature indicates that there are

phenomena that in all likelihood are examples of HTRS but that have not been interpreted as involving the process of sensitization and of CNS neuroplasticity. Two good examples are the effects of the induction of hypertension by prolonged systemic administration of very low doses of ANG II and of the phenomenon of the rapid expression of hypertension following renal artery clipping-unclipping and re-clipping.

Large doses of ANG II administered systemically are well known to produce a rapid rise in blood pressure. However, in the mid-1960s, studies in the rabbit interestingly demonstrated that maintained infusions of very low doses of ANG II that initially produced no notable rise in blood pressure would after several hours or days produce frank hypertension[119,120]. This is in spite of the fact that circulating levels of ANG II were likely to reach study-state within a few minutes. This so-called slow-pressor effect of ANG II has been demonstrated in many species (including, dog[121], rat[122], mouse[123], sheep[124] and humans[125]). The capacity of the maintained administration of low doses of ANG II to progressively shift the dose-response curve upward and produce a greater rise in the blood pressure response was originally defined as "angiotensin auto-potentiation" [126,127]. Now after recognizing that the hypertensive response can be sensitized, perhaps a more logical interpretation of the slow-pressor effect of ANG II and a mechanistic clarification of the concept of auto-potentiation is that as the low-slow pressor dose infusion of ANG II proceeds, a sensitized state is progressively being induced that reinforces and amplifies the ongoing rise in blood pressure.

Constricting renal arteries by various methods, including using small metal clips, produces hypertension over the course of several days. In rats with established two-kidney, one-clip renal hypertension (2K-1C), removal of the renal clip rapidly restores blood pressure to normal levels. However, re-clipping the renal artery a short time after its removal very quickly reestablishes the hypertensive state[128,129]. This reinstated hypertension occurs much more rapidly than the time it took to make the animals hypertensive with the original placement of the renal clips. Also shortly after the renal artery clips are removed or the clipped kidneys are ablated the pressor responses to exogenous renin or ANG II is significantly enhanced[128–130]. Notably, one unclipping-reclipping experiment implicated the CNS by demonstrating that after destroying the spinal cord there was no greater renin-induced pressor response in acutely unclipped 2K-1C rats[129]. Taken together, the clipping/unclipping/reclipping studies indicate that a control of cardiovascular function behaved as if it had a memory for a condition induced by renal clipping. Because the 2K-1C rat model of renal HT chronically increases circulating renin[129], it is probable that an initial rise in ANG II acted through neuroplasticity to reprogram the CNS to trigger a sensitized HT response when the renal artery was re-clipped or exogenous renin-angiotensin was administered. Examination of the re-clipping and slow-pressor response phenomena in the context of recognition of HTRS invites investigations examining the nature of central neuroplasticity associated with the maintenance of the sensitized state.

## Neuroplasticity accompanying hypertensive response sensitization

One of the advantages of using the IND-DEL-EXP protocol to investigate HTRS is that cellular and molecular changes in the CNS can be examined in control and experimental groups at the end of either the delay or expression phases Being able to collect tissue

samples at the end of the delay phase is an especially important asset because the blood pressure of the experimental group is still normal and not different from that of the control group. This situation obviates any concern that results might be confounded by the differing levels of hypertension in the control and experimental groups, as is the case for samples collected at the end of the expression phase. Studies of mRNA and/or protein expression in the lamina terminalis and paraventricular nucleus at the end of the delay phase have proved to be particularly informative, because they indicate molecular changes that are sustained after induction. (FIG. 3)

In every HTRS model studied to date using the IND-DEL-EXP paradigm, mRNAs related to components of the RAAS are upregulated at the end of the delay phase[1,2,131–135]. Evidence most consistent has been the observation of upregulation of AT1 mRNA. This finding is compatable with many other in vivo and in vitro studies showing upregulation of AT1 or increased binding of ANG II to AT1 after treatments that elevate levels of ANG II[136–142], or after administration or mineralocorticoid agonist[143–146]. These observations are particularly important, because for most agonist-receptor interactions, increasing the concentration of a ligand will typically produce downregulation of its receptor. The functional significance of agonist-induced receptor upregulation in the RAAS is that it can function as a feed-forward mechanism that presumably would result in response amplification and contribute to HTRS.

Recognizing that very low doses of ANG II can sensitize the hypertensive response by reprogramming the CNS to make it more responsive to ANG II may help explain the long-standing therapeutic enigma observed in the treatment of many patients with essential hypertension. Specifically, HTRS and central neuroplasticity may help address the question of why RAAS antagonists are successful in lowering blood pressure in individuals with normal- or low- plasma renin activity[147,148]. In light of demonstrations of enhanced sensitization to ANG II and indications of neuroplasticity that includes upregulation of central AT1, it seems reasonable to speculate that in such patients prior exposure to challenges may have produced an increased the number of AT1 in the CNS to manifest HTRS. Consequently, the actions of RAAS antagonists to attenuate RAAS actions in the CNS would be more effective in reducing sympathetic tone and lowering blood pressure even in normal- or low- renin patients.

Sensitization is a form of non-associative memory. The study of the cellular and molecular basis of sensitization has significantly advanced knowledge about the nature of neuroplasticity underlying learning and memory[94,149]. The maintained molecular changes observed after HTRS induction in addition to those in the RAAS indicate that the neuroplasticity associated with HTRS are similar to those found in many other models of associative and non-associative learning and memory (FIG. 3). For example, in experiments that examined the effect of non-pressor doses of either ANG II or aldosterone given during induction of HTRS on growth factors in the lamina terminalis at the end of the delay phase, brain-derived neurotrophic factor mRNA and protein levels were increased, whereas vascular endothelial growth factor mRNA and protein levels remained unchanged[136–142,150]. Also, lamina terminalis tissues collected at the end of the delay phase showed no net increase in levels of the second messenger p38 mitogen-activated protein kinase (MAPK)

nor transcription factor cyclic AMP-responsive element-binding protein (CREB). However, levels of the phosphorylated forms of each of these proteins increased significantly[150].

Collectively, the characterization of several of sustained changes following the delay phase in components of the RAAS and other molecular indictors of synaptic plasticity is consistent with the idea that there is neuroplasticity in the neural network controling sympathetic tone and blood pressure (FIGS. 2 & 3). These changes are likely to represent an instantiation of memories of earlier life challenges that produced a neural state resulting in HTRS.

## Cross-sensitization

Cross-sensitization describes the development of HTRS despite the stimulus used during the induction phase being different from that used during the expression phase. Aldosterone and ANG II interact cooperatively in the brain, indicating that both mechanisms must be intact for hypertension to occur in response to systemically administered ANG II or aldosterone[151,152]. Cross-sensitization was first confirmed by the results of IND-DEL-EXP studies, in which subcutaneous aldosterone given at a non-pressor dose during the induction phase led to HTRS when a slow-pressor dose of ANG II was administered at the beginning of the expression phase[2]. Evidence that the CNS is involved in cross-sensitization was provided by further experiments showing, first, that intracerebroventricular administration of aldosterone at a non-pressor dose during induction produced cross-sensitization when a slow-pressor dose of ANG II was delivered during the expression phase. Second, that intracerebroventricular administration of a mineralocorticoid receptor antagonist along with subcutaneous aldosterone during induction blocked HTRS[2].

Many different stressors can act to cross-sensitize with ANG II to induce HTRS in IND-DEL-EXP experiments (TABLE 1). In the course of studying these stressors, our research group has also found many interventions that can block HTRS, some of which actually reverse the sensitized state (TABLE 2). The results of these studies provide insights into the nature of HTRS and into how it might be maintained by neuroplasticity (FIGS. 1 and 3). The Information that can be derived by varying the parameters applied during induction and expression phases and by changing the duration of the delay phase is illustrated by some examples of these studies, below.

**High dietary fat intake and the role of central leptin and inflammation.—**The current obesity epidemic makes it clear that increased adiposity is a major risk factor for hypertension. Obesity and consumption of a high fat diet are both widely accepted to produce a chronic state of low-grade inflammation in the CNS, which is characterized by increased activation of microglia and astrocytes, and increased CNS expression of genes encoding pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β)[153]. Increased CNS levels of pro-inflammatory cytokines also contribute to elevated SNS activity in obesity[154].

Growing evidence from human and animal studies indicates that activation of the RAAS is involved in the pathogenesis of both obesity and obesity-related hypertension[155]. Increased ANG II levels during diet-induced obesity (DIO) activate NADPH oxidase via AT1, leading to increased production of reactive oxygen species and further increased transcription of genes encoding pro-inflammatory cytokines[155]. Thus, the RAAS and pro-inflammatory

cytokines mutually reinforce each other's actions in the periphery and in the CNS to generate sympathoexcitation and hypertension[156,157].

Results from clinical trials suggest that in addition to its anti-hypertensive effects, pharmacological inhibition of the RAAS also protects against the development of DIO and type 2 diabetes mellitus[158]. Obese Zucker rats show increased sensitivity to the blood-pressure-elevating effect of ANG II, and RAAS blockade lowers blood pressure in obese rats more than it does in lean rats, despite the obese animals having lower plasma renin activity than their lean counterparts[159]. In rabbits, 3 weeks of a high-fat diet led to increases in blood pressure, heart rate and renal sympathetic nerve activity, and this model of obesity-induced hypertension is known to be of neurogenic origin[160–162]. Interestingly, although animals with DIO placed on a normal diet were able to restore their body weight, insulin levels and leptin sensitivity to normal, their blood pressure, renal sympathetic nerve activity and levels of central RAAS components and pro-inflammatory cytokines remained high[163]. These results indicate that obesity itself might induce hypothalamic inflammation and sensitization of the brain to circulating sympathoexcitatory factors (such as those from the RAAS) and that these factors might drive hypertension.

In light of the relationship between obesity and essential hypertension and the need to understand how adiposity results in high blood pressure, our group conducted IND-DEL-EXP experiments to test whether a high-fat diet could produce HTRS. Rats were placed on a high-fat diet for 3 weeks (the induction phase). At the end of this period, body weight, white adipose tissue mass and plasma leptin levels were all increased. Tissue samples from the lamina terminalis showed increased levels of mRNAs encoding components of the brain RAAS (namely, renin, ACE and AT1), the pro-inflammatory cytokines TNF-α and IL-6, and a marker of microglial activation (CD11b)[131]. In parallel experiments, animals on the high-fat diet for three weeks were then returned to a normal diet and immediately challenged during an expression phase with a slow-pressor dose of ANG II. This evoked HTRS in the animals that had been on the high-fat diet. Taken together, these results suggest that a high-fat-diet-induced upregulation of the RAAS and pro-inflammatory cytokines in the CNS, which participated in the induction of HTRS. The capacity of the RAAS and pro-inflammatory cytokines to mutually upregulate their expression is an important factor in central feed-forward pathways that induce HTRS.

In obese humans and in animal models of DIO, increased SNS activity and high blood pressure are both associated with increased levels of leptin and activation of the leptin–melanocyte stimulating hormone-α–melanocortin receptor 4 pathway[164,165]. Brain structures that mediate the central actions of leptin include the arcuate nucleus (ARC), PVN, SFO and hindbrain. Microinjection of leptin into the ARC or PVN resulted in increased SNS activity[166,167], whereas deletion of the leptin receptor (LEPR) in the ARC or SFO attenuated this leptin-elicited increase in SNS activity[166,168]. Leptin-deficient or LEPR-deficient mice demonstrate attenuated microglial activation and reduced levels of inflammatory mediators[169], findings that are consistent with leptin having a pro-inflammatory function. Furthermore, a high-fat diet and obesity both activate microglia and astrocytes and increase levels of pro-inflammatory cytokines in the SFO and PVN[170]. These effects are ANG II-dependent, as some responses are reversed by deletion of AT1 in the PVN[170]. SNS

responses to leptin are also dependent on central AT1, as intracerebroventricular infusion of losartan attenuated SNS activity in response to leptin[171]. Additional evidence indicates that obesity-associated activation of the hypothalamic inflammatory pathway mediates the CNS functions of leptin[172]. These findings suggest that the interactions and synergism between leptin, the RAAS and pro-inflammatory cytokines are responsible for the increase in SNS activity that occurs early in the onset of obesity.

Obesity, a high-fat diet, leptin, pro-inflammatory cytokines and microglial interactions all have a role in HTRS. In IND-DEL-EXP experiments, central administration of leptin during the induction phase mimicked the HTRS-inducing effects of a high-fat diet, whereas intracerebroventriclar administration of a leptin receptor antagonist prevented the induction of HTRS by 3 weeks of a high-fat diet[134]. Intracerebroventricular TNF-α was as effective in inducing HTRS as intracerebroventricular ANG II given at a non-pressor dose. TNF-α given during the induction phase resulted in increased levels of mRNAs encoding components of the RAAS and increased levels of markers of inflammation and microglial activation in lamina terminalis structures[131]. Central inhibition of AT1, TNF-α synthesis or microglial activation all blocked the induction of HTRS by either leptin or high fat diet. These inhibitors also blocked the upregulation of RAAS activity and the rise in indicators of inflammation in the lamina terminalis[131,134].

Taken together, the results of these studies provide insight into the role of metabolic factors and the actions of the brain RAAS and the brain innate immune system that mediate the production of HTRS. Accordingly, we hypothesize that eating a high-fat diet increases the effects of leptin on and in the brain, which activates the brain RAAS and upregulates inflammatory mechanisms that result in reprogramming the control of SNS activity and HTRS (FIG. 4). The consequence of these changes is that HTRS increases the likelihood that frank hypertension will develop if these challenges are sustained or when additional hypertensinogenic stressors are encountered later in life.

**Gestational hypertension and maternal high dietary fat intake.—**Maternal health during pregnancy is strongly associated with the cardiovascular health of her adult offspring. Many studies have demonstrated that the offspring of mothers with gestational hypertension have increased blood pressure in childhood and adolescence, and that these children are at an increased risk of developing hypertension in adulthood[173–178]. This risk to the offspring is graded and greatest in those whose mothers had the most severe hypertensive signs, such as early onset hypertension or pre-eclampsia[177,179]. Animal experiments also demonstrate that many kinds of prenatal insult, including uteroplacental insufficiency, protein restriction, chronic secondary hypertension and glucocorticoid treatment during pregnancy, lead to hypertension in the offspring[180].

Increased renal sympathetic nerve activity and over activity of the RAAS and pro-inflammatory cytokines in the periphery have been implicated as causal mechanisms in prenatal programming of hypertension. In human studies, the adolescent sons of mothers who had high blood pressure during pregnancy had increased aldosterone levels, a trend towards increased circulating renin activity, and increased SNS activity before and during isometric exercise[181,182]. In animal models, renal denervation or chronic blockade of both

the RAAS and inflammation reduced hypertension (via restoration of renal and arterial function) in the offspring of dams that had received different types of insult during pregnancy[183–187]. The RAAS has a key role not only in the generation of increased basal blood pressure but also in the development of enhanced renal sympathetic and pressor responses to physical stress observed in male offspring of pregnant dams exposed to protein restriction[188,189].

Besides exploring the roles of the peripheral RAAS and sympathetic nerve activity in the development of hypertension in prenatally programmed hypertensive animals, a few studies have implicated the brain RAAS in hypertension associated with antenatal nutrient deprivation. Intracerebroventricular injection of an ACE inhibitor or an AT1 antagonist significantly reduced the blood pressure of animals previously subjected to maternal protein restriction in utero. Expression of AT1 in the SFO and the OVLT was increased in these animals compared with controls[190].

The time between prenatal interventions and the development of hypertension in adult animals is long compared to the delay periods used in our IND-DEL EXP studies of HTRS. Consequently, these studies have provided a good way to investigate the duration of HTRS. Prenatal induction of HTRS was accomplished by subjecting pregnant dams to ANG II-elicited gestational hypertension. The adult male offspring of these dams had normal resting blood pressures but showed HTRS when challenged with a slow-pressor dose of ANG II during a 2-week expression phase, which began when the rats were 10 weeks old[191]. Protein and/or mRNA expression of components of the RAAS, markers of microglial activation and brain levels of pro-inflammatory cytokines (which indicate activation of the brain's innate immune system) were also increased in these offspring[191]. These experiments demonstrate that reprogramming of the mechanisms controlling SNS activity and blood pressure during the prenatal period produces long-lasting phenotypic changes in the CNS as well as sensitized responsiveness to a hypertensinogenic challenge during adulthood.

Various interventions during the delay period (that is, between weaning of these rats at 3 weeks of age and pressor challenge at 10 weeks of age) can abrogate HTRS. For example, in one experimental group, the ACE inhibitor captopril was administered in the drinking water beginning from weaning until the rats were 8 weeks old. Another experimental group underwent renal denervation at 8 weeks of age. Both interventions blocked HTRS in 10-week-old male offspring of dams with gestational hypertension. Consistent with these findings, the upregulation of mRNAs encoding components of the brain RAAS and indices of CNS inflammation also were normalized in captopril-treated animals[191].

As noted above, many human and animal studies have found that female subjects in comparison to male offspring are frequently protected from the effects of negative earlier life experiences producing hypertension later in life. We have also seen that females are protected against the induction of HTRS[192,193]. Unfortunately, an in-depth discussion of the nature of the female-related protection against HTRS and the role of estrogen and other anti-hypertensive factors prominent in females is precluded by space limitations placed on the present review.

In humans as well as in experimental animals, maternal obesity and maternal high dietary fat intake have adverse consequences for health of her offspring by altering their responses to environmental challenges and predisposing them to cardiovascular and metabolic disease[194–197]. For example, the offspring of rabbits fed a high-fat diet have elevated renal sympathetic nerve activity and pressor responses to central leptin, increased sympathetic responses to ghrelin and an exaggerated sympathetic response to acute air-jet stress[198]. These observations suggest that the elevations in blood pressure and renal sympathetic nerve activity are attributable to changes in central pathways that regulate SNS activity[198]. Also, a maternal high-fat diet has been associated with hypothalamic inflammation, impaired baroreflex sensitivity and reduced heart rate variability in the offspring, implicating abnormalities in autonomic control[199–201]. The effects of maternal obesity and a maternal high-fat diet on HTRS, and the influence of a maternal high-fat diet on the autonomic function of her offspring have been studied in female rats fed a high-fat diet beginning 8 weeks before conception and continuing throughout either pregnancy and lactation, just during pregnancy, or just during lactation[135]. The 10-week-old adult offspring of these rats, which had initially normal blood pressure, showed a blunted cardiac baroreflex and an elevated autonomic responsiveness of blood pressure and heart rate to an acute challenge with either intracerebroventricular ANG II or TNF-α[135]. These offspring also showed upregulated mRNA expression of RAAS components and increases in levels of NADPH oxidase and pro-inflammatory cytokines in the lamina terminalis and PVN in response to being challenged with a slow-pressor dose of ANG II during the expression phase[135].

Taken together, these results indicate that a maternal high-fat diet during either pregnancy or lactation is sufficient for early-life reprogramming of the central neural network controlling SNS activity and blood pressure, thereby producing HTRS and predisposing the offspring to an increased risk of hypertension in adulthood.

The perinatal period has long been recognized as a critical time during which many interventions are particularly effective in reprogramming many physiological systems and particularly the nervous system[202,203]. One of the consequences the presentation of challenges to offspring via the mother is that it can induce a sensitized state that is maintained and that can be expressed as hypertension when exposed to stressors much later in life. Perinatal challenges presented to the offspring represent a predisposition for expressing hypertension that are likely to last a lifetime.

**Psychosocial stressors.—**Social defeat is an example of a psychosocial stressor that can induce HTRS when administered in a resident-intruder experimental paradigm. These experiments involve introducing a smaller adult male rat, the intruder, into the cage of a larger male, the resident, who is well established in his living quarters. During such pairings, the two animals reliably take on different behavioural roles. The resident immediately assumes the role of the dominant animal and the intruder becomes submissive and displays psychosocial defeat. In addition to behavioural submission, the defeated intruder manifests cardiovascular changes typical of reactions to stressors[204].

This paradigm is considered to be an excellent model of post-traumatic stress disorder (PTSD), a psychiatric illness characterized by persistent emotional and mental stress

following traumatic events[205,206]. Patients with PTSD are at increased risk of developing hypertension and cardiovascular disease[207,208]. Both patients with PTSD and animal models of PTSD are characterized by increased SNS activity, decreased cardiac vagal control and baroreflex dysfunction[207–212]. Enhanced sympathetic activity and blunted baroreceptor reflex sensitivity is also associated with elevated levels of pro-inflammatory cytokines and activation of the peripheral and brain RAASs[213,214].

Three resident-intruder pairings (made every other day during a 1-week induction period) followed by a 3-day delay period reliably produced HTRS in the intruder. In addition, lamina terminalis tissue collected at the end of the delay period showed increased mRNA expression of AT1, IL-1β, IL-6 and TNF-α[132]. Pretreatment with captopril or administration of a TNF-α antagonist during the induction period abrogated the HTRS produced by resident-intruder pairings, and also blocked the increased expression of RAAS components and proinflammatory markers in the brain[133].

The results of these resident-intruder studies provide insight into the mechanisms by which psychosocial stress, such as that associated with PTSD, induces HTRS. Information derived from such studies will be useful in generating new therapeutic strategies for patients with mental health and cardiovascular disease comorbidities.

**Salt-sensitive hypertension.—**High dietary sodium chloride (table salt) intake is widely viewed to be a contributor to the pathogenesis of hypertension[215–217]. The effect of high salt intake on blood pressure varies between individuals in both humans and nonhuman species, as environmental and genetic factors both contribute to salt sensitivity[215,218,219]. Rigorously defined protocols have been developed to diagnose salt sensitivity[215,220], and it is estimated that in the United States, about 51% of patients with hypertension and about 26% of normotensive individuals are salt-sensitive[221].

Growing evidence indicates that the brain is involved in the control of both sympathetic tone and salt sensitivity[221–225]. Accordingly, the effects of systemic ANG II or aldosterone administration were studied in IND-DEL-EXP experiments to see if these hypertensinogenic challenges would produce salt sensitivity[150]. Rats were implanted with probes to enable continuous recording of blood pressure and heart rate. After recovery from surgery, they received 1 week of systemic treatment with either vehicle or non-pressor doses of either ANG II or aldosterone (the induction phase). After a 1-week delay period, the rats were given 2% saline as their sole drinking fluid[226,227]. Blood pressure increased significantly from baseline in all animals; however, the increase was significantly greater in the groups that had previously received ANG II or aldosterone. Blood pressure in all three groups fell to pre-exposure levels when saline was replaced with plain water. Additional studies found that salt sensitivity can also be produced by intracerebroventricular administration of non-pressor doses of either ANG II or aldosterone during a 1-week induction period.

The finding that salt sensitivity can be experimentally induced is important for two reasons. First, these experiments show that HTRS can be demonstrated during the expression phase by using a treatment (high salt intake) other than a slow-pressor dose of ANG II. Second, they demonstrate that the expression of salt sensitivity does not require a genetic

predisposition or the administration of another pressor agent in conjunction with high salt intake. The CNS can be programmed to display HTRS when excessive amounts of sodium are subsequently consumed.

## The functional relevance of adaptation

Substantial evidence from HTRS studies implicates the brain RAAS in reprogramming of the central neural network that controls SNS activity and determines long-term blood pressure regulation. The observation that stressors induce a sustained upregulated expression of components of the RAAS is of particular importance, as this feed-forward mechanism is critical for the memory-related processes that mediate HTRS. However, the brain RAAS is not the only system that includes mechanisms for long-term information storage.

The acquired or adaptive immune system employs T and B memory cells to quickly and specifically recognize an antigen the body has previously encountered, which enables the initiation of a corresponding immune response. However, several components of the innate immune system[228], including brain microglia[229], also have memory capacities, and this newly recognized function of the innate immune system in the brain brings neurological and immune memory mechanisms in close proximity to one another. The emerging picture of mechanisms involved in HTRS is that microglia and pro-inflammatory cytokines are as likely as the brain RAAS to have important roles in inducing and maintaining HTRS (FIG. 4). Essentially, these mechanisms predict future events, a theme that is explored further below.

### Phenotypic plasticity

The concept of phenotypic plasticity is related to the likelihood that a given genotype will produce different phenotypes under varied environmental conditions[230]. In many physiological and behavioural systems, response sensitization is advantageous for defending an organism's integrity against the consequences of recurring challenges. For example, immune memory enables a more rapid, amplified response to be generated against a previously encountered pathogen. Rather than strict adherence to information carried in the genome, phenotypic plasticity involves mechanisms that alter genetic expression and neuroplasticity. Under some — but not necessarily all — conditions, the consequence of phenotypic plasticity is increased biological fitness.

### Selection pressure and mismatch

Many species spent much of their evolutionary history under environmental conditions that posed a constant threat of circulatory collapse[217]. Acute extracellular fluid losses — from injury-induced blood loss, from pathogen-induced emesis and/or diarrhoea, and water and sodium loss via perspiration were (and still are) frequent threats to survival in hunter-gatherer populations in the hot African savanna. Furthermore, under natural conditions, full recovery from severe hypovolaemia requires the behavioural competence necessary for acquiring adequate amounts of water and sodium, which are both necessary for restoring extracellular volume and for maintaining blood pressure. Access to these commodities can be severely limited, especially during a prolonged dry season. For an individual living under

such circumstances, survival of a hypovolaemic challenge might require adaptations that favour a phenotype that maintains blood pressure and staves off uncompensated hypovolaemic shock. Therefore, the capacity to enhance a sympathetically driven hypertensive response, mediated by neuroplasticity and CNS reprogramming, would confer biological fitness in an ecological niche where hypovolaemic shock and circulatory collapse had a high probability of occurrence. However, under different circumstances, such an environmentally triggered phenotypic adaptation might contribute to the pathogenesis of hypertension.

Essential hypertension and related cardiovascular diseases are pathologies of old age. At the time in human evolutionary history when selection for a phenotype that conferred protection against hypovolaemia and hypotension presumably occurred, the life span of most individuals was probably 30–40-years[231], and morbidity and mortality from cardiovascular disorders would be limited. Moreover, as individuals would not develop hypertension and its consequences until after their prime reproductive years, the selection pressure for mechanisms that promoted survival in the face of circulatory shock would be greater than that exerted by the manifestations of cardiovascular disease in aged individuals.

Ambient conditions, at least in western societies, have changed dramatically since this selection for what was once an adaptive trait. This fact is particularly relevant in considering the functions of the RAAS, a system whose major components have been present since the divergence of bony fishes (about 400 million years ago)[232]. The interest in the RAAS for countless researchers and clinicians has been its role in body fluid homeostasis and blood pressure control. By contrast, the role of the RAAS as a major mediator of the stress response has received relatively little attention. Stressors increase activity in both the systemic and brain RAASs (reviewed elsewhere[233]). The RAAS is readily activated not only by challenges that produce hypovolaemia and blood pressure dyshomeostasis, but also by a wide range of stressors, including academic examinations[234], restraint[235], immobilization[236], avoidance conditioning[237], swimming[238], pain[238], hypoglycaemia[239] and chronic mild stress[240]. Cumulative activation of the systemic and/or brain RAAS might induce a progressively greater and greater sensitized state of the CNS, and when sufficiently intense or sustained hypertensinogenic challenges are present (or when counter-regulatory or protective mechanisms begin to fail, as they do in ageing individuals), frank essential hypertension ensues. Thus, if plasticity-promoting phenotypic change was indeed incorporated into the ancestral human genome to protect against hypovolaemic shock, this trait may now have become a liability.

## Conclusions

In summary, the recognition that a wide range of physiological and psychosocial challenges to actual or perceived potential homeostatic disruption can lead to HTRS provides a new paradigm for considering the causes and course of essential hypertension. Experiencing repeated challenges or stressors over the course of a lifetime can leave their mark by introducing neuroplastic changes in the brain network controlling sympathetic tone and blood pressure. By employing the IND-DEL-EXP experimental model, we have been able to begin to characterize the nature and range of stressors that induce HTRS and to investigate

the sites of cellular and molecular neuroplasticity that relate the encoding of earlier events to the ongoing control of sympathetic tone and blood pressure.

One might be discouraged by realizing that stressor-induced insults are maintained as memories in the CNS and that the probability of expressing frank hypertension increases as time passes (TABLE 1). However, a basis for optimism remains, as pharmacological, surgical or behavioural interventions might be able to reverse the mediators and the expression of HTRS (TABLE 2).

The number of studies using the IND-DEL-EXP paradigm that link changes in the neural control of the circulation to mechanisms involving sensitization of the hypertensive response is as of yet small and the work is in its infancy. The recent demonstration of the phenomenon of HTRS and the identification of some accompanying indicators of CNS neuroplasticity allowing a sensitized state to be maintained over extended durations raises many new questions that need to be answered. Some examples of such new issues are presented in TABLE 3. Addressing many of these questions will provide deeper insights into the causes, treatment and prevention of essential hypertension.

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## GLOSSARY

**Response sensitization**
Sensitization is operationally defined and occurs when repeated administration of a stimulus results in an increase in the magnitude of a response.

**General adaptation syndrome**
A term describing the three predictable stages of behavioural and physiological responses to stressors. The 'alarm reaction' stage provides a burst of energy to deal with the onset of a stressor. In the 'resistance' stage, the body attempts to overcome or adapt to the stressor. Maintenance of the resistance stage is hypothesized to lead to 'exhaustion', associated with depletion of bodily resources, morbidity and mortality.

**Stressor**
A threatening or noxious stimulus that produces a stress response and is associated with state defined as stress (i.e., an inferred state or hypothetical construct).

**Classical or Pavlovian conditioning**
A learning paradigm first developed by the physiologist Ivan Pavlov. A biologically potent stimulus (such as food or an electric shock) is paired with a previously neutral stimulus (such as a tone or light). Pairing produces an association between the two stimuli, such that the neutral stimulus comes to elicit a response similar to that originally produced by a prepotent stimulus.

**Limbic system**
An extensive set of phylogenetically old, interconnected brain structures located in the rostral part of the nervous system (forebrain). The limbic system was originally identified as a functional system related to emotion. Today, limbic structures are implicated in the control of many physiological, behavioural and cognitive functions.

**Lamina terminalis**
The single layer of ependymal cells that form the rostral wall of the third cerebral ventricle. Four structures — the subfornical organ, median preoptic nucleus, the organum vasculosum of the lamina terminalis and the anterior commissure — lie immediately rostral to the lamina terminalis and are often, albeit technically erroneously, commonly referred to as the lamina terminalis.

**Neuromodulator**
A substance released by neurons that acts to increase or decrease the actions of neurotransmitters. Neuromodulators affect large numbers of neurons by acting in a diffuse paracrine fashion, in contrast to the tight coupling between neurons using synaptic neurotransmitters to communicate.

**Cytokines**
Proteins that are important in autocrine, paracrine, and endocrine signaling, particularly in the immune system. Pro-inflammatory cytokines promote inflammation whereas anti-inflammatory cytokines reduce inflammation. Adipokines are cytokines secreted by adipose tissue.

**Long-term potentiation**
The strengthening of synapses that results from increased neural activity. Long-term potentiation facilitates synaptic transmission between adjacent neurons.

**Operant conditioning**
Also known as instrumental conditioning. A type of learning in which a response is modified by positive or negative reinforcement: that is, by association with the presentation of either a reward (such as food) or a punishment (such as electric shock).

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**Key points**

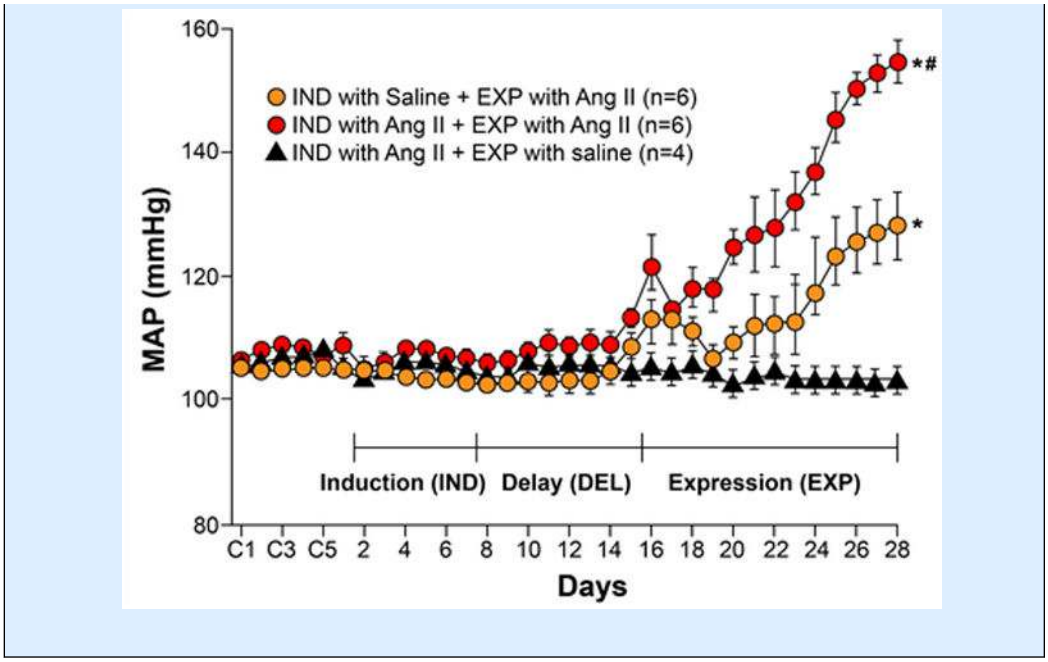
- The aetiology of essential hypertension is still unknown.
- Emerging evidence has shown that the hypertensive response can undergo sensitization.
- Hypertensive response sensitization (HTRS) involves neuroplasticity induced by a wide range of physiological and behavioural challenges (stressors) occurring throughout life.
- The cellular and molecular changes that mediate HTRS are located and maintained in the central neural network that controls sympathetic nervous system activity.
- The neuroplasticity of the sympathetic nervous system provides adaptive blood pressure control, such that an increased hypertensive response (to physiological or psychosocial stressors) is learned and subsequently remembered.
- Recognition of HTRS and the centrally mediated mechanisms driving the sensitized state provides a new paradigm for understanding essential hypertension and developing new strategies for its prevention and treatment.

**Box 1:**

### Experiments showing hypertensive response sensitization.

In induction-delay-expression (IND-DEL-EXP) experiments, a stimulus is presented during an induction phase typically lasting 1–3 weeks. Subsequently, the individual is challenged with the same or another stimulus, and the magnitude of the elicited response is measured during the expression phase, which generally lasts 2 weeks. Depending upon the experiment, the interval between induction and expression is of variable duration (ranging between no delay and many weeks), and is referred to as the delay phase.

The above illustration shows typical findings from an IND-DEL-EXP experiment showing hypertensive response sensitization (HTRS)[1]. Three groups of adult male rats underwent implantation of telemetry probes to enable continuous recording of blood pressure and heart rate. After recovery from surgery, the animals received either saline or subcutaneous angiotensin II (ANG II) 10 ng/kg/min. The induction and delay phases each lasted 1 week. Blood pressure usually changes little during the induction phase; a transient increase in blood pressure can occasionally be seen in some models, but always returns to baseline before the start of the expression phase. The delay phase enabled the persistence of the effects of HTRS Induction to be assessed and any remaining exogenous ANG II to be metabolized. At the beginning of the expression phase, the rats received a further stimulus with either saline or subcutaneous ANG II 120 ng/kg/min. As this slow-pressor dose of ANG II does not immediately elicit hypertension, the initial rise in mean arterial blood pressure (MAP) seen in animals that received ANG II over the first 3–4 days of the expression phase probably represents the systemic vasoconstrictor action of ANG II. After 4 days the vasoconstrictor effect of ANG II is replaced by increased sympathetic drive, which continues to increase blood pressure[241]. $*P<0.05$ versus baseline, or versus induction with ANG II then expression with saline. $^{\#}P<0.05$ versus induction with saline then expression with ANG II. Figure redrawn and based on data presented in [1].



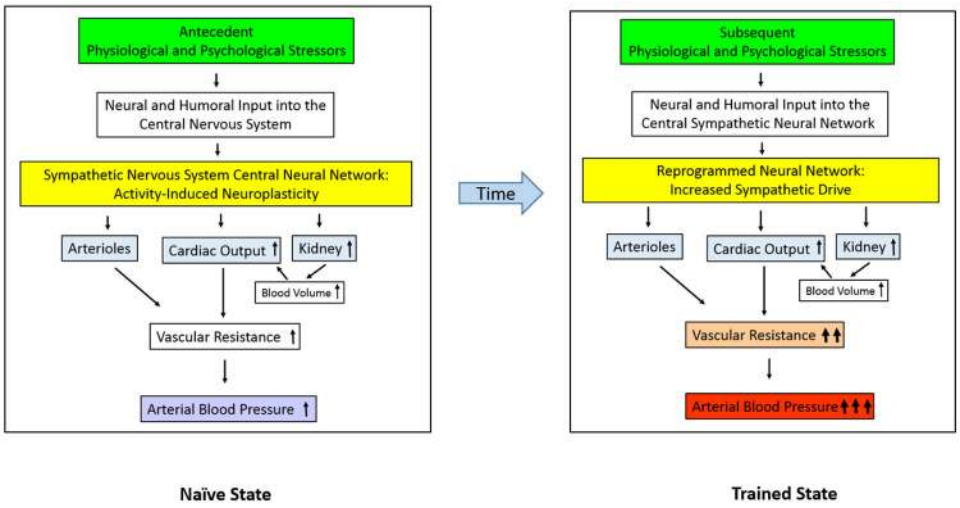



**Figure 1: The hypothetical role of neuroplasticity and hypertensive response sensitization in the aetiology and progression of essential hypertension.**

**Left|** In the stimulus-naive state, exposure to stressors earlier in life activates the central neural network that controls sympathetic nervous system tone and raises blood pressure. Over time, repeated exposure to the stressors result in activity-driven neuroplasticity, which reprograms the central sympathetic neural network to increase sympathetic drive. **Right |** In the trained state, stressors produce increased sympathetic drive, which results in increased vasoconstriction and/or increased blood volume and cardiac output. Collectively, these changes trigger an increase in vascular resistance[33–35]. If the increase in vascular resistance is sustained, vascular remodeling and chronic hypertension result.

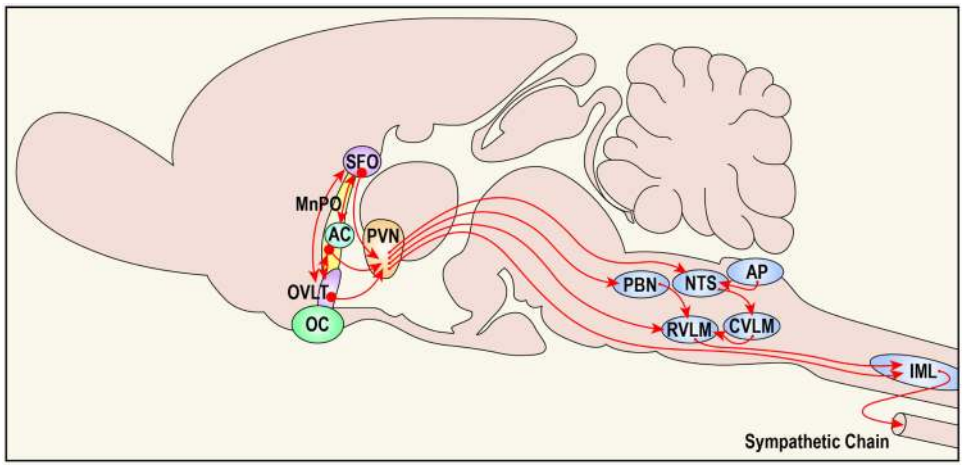



**Figure 2: A midline schematic representing the circuitry of a portion of neural network controlling sympathetic tone and blood pressure regulation.**

Activation of the neural pathways arising from rostral structures located along the lamina terminalis and running caudally to the spinal cord are normally activated by the physiological stressors of falls in blood volume and blood pressure. In components of the neural network, structures located along the lamina terminalis [i.e., subfornical organ (SFO), median preoptic nucleus (MnPO), organum vasculosum (OVLT)] and the hypothalamic paraventricular nucleus (PVN) have been implicated as structures where stressors produce neuroplasticity that mediates a sensitized hypertensive response.

The SFO is the primary forebrain target for ANG II and cells in the OVLT function as osmo- or $Na^+$ -receptors. The MnPO, which lies inside the blood-brain barrier, receives input from both the SFO and OVLT and probably functions to process information about the status of intracellular and extracellular fluid compartments and blood pressure. The SFO, MnPO, and OVLT all provide input to the PVN. In turn, the PVN integrates this information with input from other sources (not shown) to influence preganglionic sympathetic neurons in the spinal cord [interomediolateral cell column (IML)] both directly and via the rostral ventrolateral medulla (RVLM). Represented are some additional areas implicated in cardiovascular control. These include the area postrema (AP), caudal ventrolateral medulla (CVLM), nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN), which either directly or indirectly influence activity in the RVLM. Additional abbreviations: AC, anterior commissure; OC, optic chiasm. (Modified Figure based on figure in reference 116)

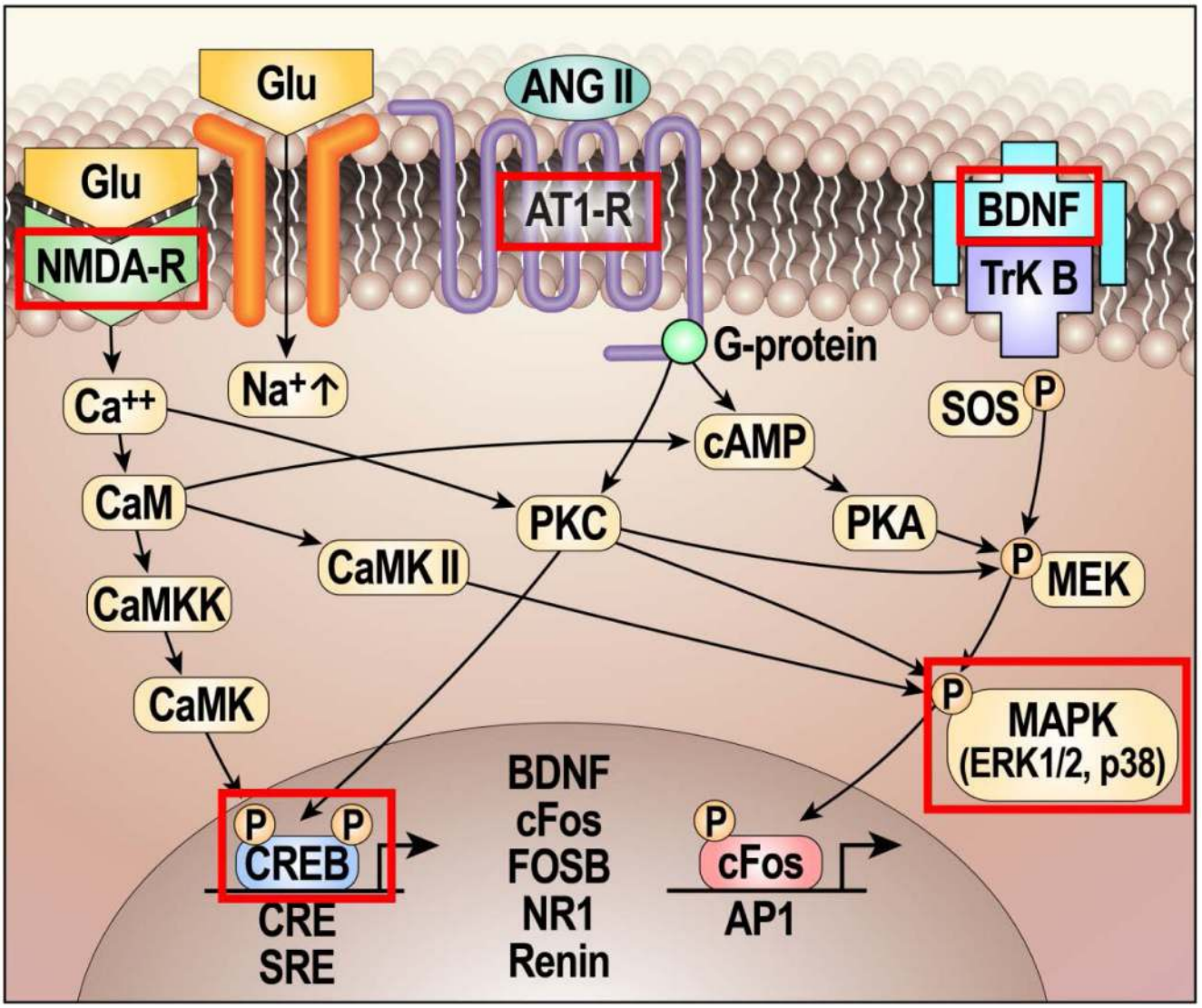



**Figure 3: Mechanisms involved in hypertensive response sensitization (HTRS) and neuroplasticity.**

By studying changes after the induction of HTRS, important memory-related molecular changes have been identified that are maintained until the end of the delay period. Many neural systems involve 'signature' neurotransmitters or neuromodulatory mechanisms. For example, substance P and calcitonin gene-related peptide and their receptors are ubiquitous in pain signaling pathways[97,98,242]. As components of the brain renin–angiotensin–aldosterone system (RAAS) are upregulated after induction of hypertensive response sensitization (HTRS), RAAS components might reasonably be considered a signature of the pathways controlling sympathetic tone and blood pressure. Considerable evidence indicates that glutamate and glutamate receptors are critically involved in nearly all forms of neuroplasticity[243,244], and most cells in the nervous system express at least one type of glutamate receptor[245]. This neurotransmitter depolarizes neurons by acting on ionotropic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Most, if not all, cells in the network controlling sympathetic tone have

both NMDA and AMPA receptors and receive glutamatergic input from other network neurons. Growth factors have multiple roles in neuroplasticity including altering membrane potentials, increasing protein synthesis, promoting cell viability, and morphological changes. Brain-derived neurotrophic factor (BDNF, probably the best-studied CNS growth factor) is associated with almost every aspect of neural and functional plasticity[246] and acts through TrkB (also known as BDNF/NT3 growth factors receptor). Finally, long-term neuroplastic changes require the synthesis of new proteins, which requires activation of transcription factors, including c-Fos, FOSB and cAMP response element-binding protein (CREB). Red rectangles indicate signaling mechanisms implicated in the neuroplasticity underlying HTRS[247]. In future work, it will be important to determine how many structures in the neural network controlling sympathetic tone and blood pressure manifest detectable changes and how long such changes persist. Figure based on and modified from REF.[116].

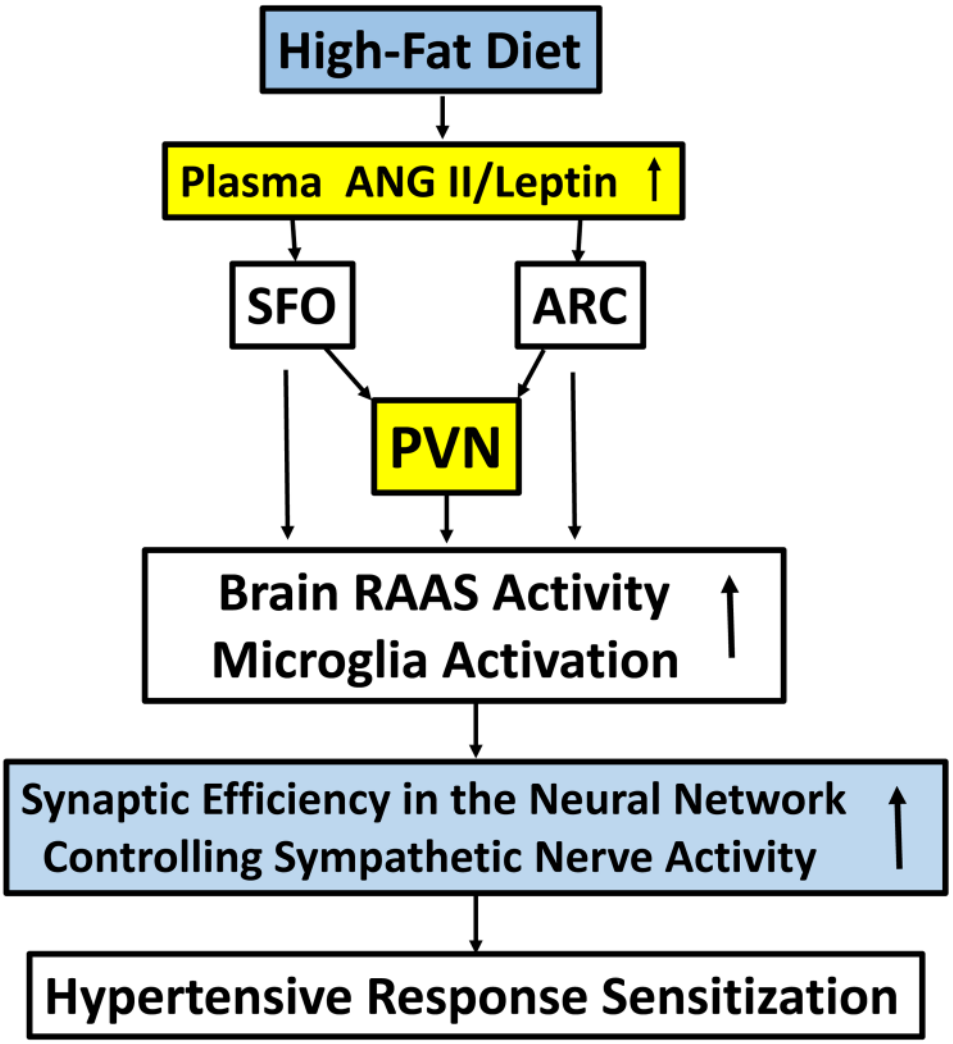



**Figure 4: How a high-fat diet and obesity might induce hypertensive response sensitization.**

High-fat diet and obesity both increase circulating levels of both angiotensin II (ANG II) and leptin. Circulating ANG II and leptin act on the subfornical organ (SFO) and/or the hypothalamic arcuate nucleus (ARC), both of which have projections to the hypothalamic paraventricular nucleus (PVN). Actions of ANG II and leptin in the SFO, ARC, and/or PVN activate the brain renin–angiotensin–aldosterone system and inflammatory mechanisms that result in inducing sensitization by increasing synaptic efficiency in the SFO and/or PVN.

**Table 1.**

Stimuli used to induce sensitization of the hypertensive response

| Stressor | Route of administration | Duration of challenge | Ref. |
|---|---|---|---|
| ***Systemic stressors*** | | | |
| Non-pressor ANG II | Subcutaneous | 1 week | 1 |
| Non-pressor ANG II | Intracerebroventricular | 1 week | 1 |
| Non-pressor aldosterone | Subcutaneous | 1 week | 2 |
| Non-pressor aldosterone | Intracerebroventricular | 1 week | 2 |
| High-sodium diet | Food | 2 weeks | 116 |
| High-fat diet | Food | 3 weeks | 131 |
| Low-sodium diet | Food | 2 weeks | 116 |
| Hypotensive haemorrhage | NA | 3 times in 1 week | 248 |
| Lipopolysaccharide | Intraperitoneal | 3 times in 1 week | Unpublished |
| Leptin | Intracerebroventricular | 1 week | 134 |
| TNFα | Intracerebroventricular | 1 week | 131 |
| ***Processive stressor*** | | | |
| Resident-intruder social defeat | External and/or psychosocial | 3 times in 1 week | 132, 133 |
| ***Perinatal challenge to offspring*** | | | |
| Maternal gestational hypertension | ANG-elicited hypertension | 3 weeks of pregnancy | 191 |
| Maternal high-fat diet | Food | 3 weeks of pregnancy | 135 |
| Maternal high-fat diet | Food | 3 weeks of lactation | 135 |
| Maternal high-fat diet | Food | 3 weeks of pregnancy plus 3 weeks of lactation | 135 |

Expression of sensitization of the hypertensive response was tested by subcutaneous administration of angiotensin II 120 ng/kg/min. ANG, angiotensin; NA, not applicable; TNF, tumour necrosis factor-α.

**Table 2.**

Treatments that block or reverse sensitization of the hypertensive response.

| Blocking treatment | Route of administration | Sensitizing challenge | Ref. |
|---|---|---|---|
| Mineralocorticoid antagonist | Intracerebroventricular | Blocks induction with subcutaneous aldosterone | 2 |
| Leptin inhibitor | Intracerebroventricular | Blocks induction with high-fat diet feeding | 134 |
| Minocycline | Intracerebroventricular | Blocks induction with high-fat diet, intracerebroventricular ANG II and intracerebroventricular leptin | 131,134 |
| Pentoxifylline | Intracerebroventricular | Blocks induction with high-fat diet, intracerebroventricular ANG II and intracerebroventricular leptin | 131,134 |
| AT1 antagonist | Intracerebroventricular | Blocks induction with high-fat diet, subcutaneous ANG II and intracerebroventricular leptin | 1,131,134 |
| Renal denervation | NA | Reverses sensitization induced by maternal gestational hypertension | 191 |
| Spontaneous exercise | NA | Delays expression of sensitization by maternal gestational hypertension | Unpublished |
| Oestrogen | Intracerebroventricular | Blocks induction with subcutaneous ANG II in male rats and ovariectomized female rats | 192 |
| Raloxifene | Intracerebroventricular | Blocks induction with subcutaneous ANG II in male rats and ovariectomized female rats | Unpublished |
| Valproate | Subcutaneous | Blocks induction with subcutaneous ANG II | Unpublished |
| Sodium butyrate | Intraperitoneal | Blocks induction with subcutaneous ANG II | Unpublished |
| Dizocilpine (MK-801) | Subcutaneous | Blocks induction with subcutaneous ANG II | 247 |
| AP-5 | Intracerebroventricular | Blocks induction with subcutaneous ANG II | 247 |
| $ANG_{1–7}$ | Intracerebroventricular | Blocks induction with subcutaneous ANG II | 192 |

ANG, angiotensin; AP-5, (*2R*)-amino-5-phosphonovaleric acid, an N-methyl-D-aspartate receptor antagonist; AT1, type-1 angiotensin II receptor; NA, not applicable.

**Table 3:**

Important Questions to be Addressed for a Better Understanding of the Role and Mechanisms of Neuroplasticity in Hypertensive Response Sensitization

| |
|---|
| • What are the limits for maintaining the sensitized state when it is induced in adult animals? |
| • How extensive is the distribution of CNS sites involved in maintaining the sensitized state? |
| • How do glial cells communicate with neuronal components in the neural network controlling the sympathetic nervous system to induce neuroplasticity and sensitization? |
| • What epigenetic changes are likely to maintain the sensitized state? |
| • How do dietary factors such as high fat or high salt intake interact with the sensitized state to produce frank hypertension in the course of ageing? |
| • In the course of ageing, are counter-regulatory mechanisms lost that buffer against the sensitized state producing a rise in blood pressure in the face of new or sustained stressors? |
| • What interventions can reverse the neuroplasticity that maintains the sensitized state and when is the best time to apply them? |