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 which 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 phenomenon 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.

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

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Environmental and physiological challenges encountered throughout one's lifetime can induce long-lasting adaptations in physiological and behavioural systems. The consequence of such experientially induced adaptations is often 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 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 the adaptive neural control of effector systems involves neuroplasticity, which 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 was recognized only recently (in 2012) as a mechanism that can become sensitized[1,2], 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.

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.

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 in either the perinatal period or 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 are introduced through a discussion of 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 to 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. The effects of SNS activation are also more rapid than those of other systems (such as endocrine, immune or behavioural responses) that are mobilized subsequently to minimize and 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 group of effects has been dubbed the fight or flight response. The term stress was used to describe both sympathetic and behavioural responses to noxious or threatening challenges[3–5]. Later research showed that behavioural and cardiovascular components of the fight or 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 hypothalamic–pituitary–adrenal axis in responses to stressors and the general adaptation syndrome[10–12].

A stressful stimulus (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 of 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, as discussed below[16–19].

Essential hypertension

Hypertension is the leading risk factor for disability and death worldwide[20,21]. High blood pressure 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 diagnosed as having hypertension, as the new threshold values for systolic and diastolic blood pressure are lower than those used previously[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.

The role of tissue perfusion

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[26]. In recognition of the fact that blood pressure is a mechanism for controlling tissue perfusion and that increased systemic vascular resistance is the proximal cause and hallmark of established

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', with depletion of bodily resources, morbidity and mortality.

Stressor
A threatening or noxious stimulus that produces a stress response and is associated with the state defined as stress (that is, 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.

essential hypertension[27,28], the mosaic theory of arterial hypertension proposed that these interacting factors were also likely to contribute to the pathogenesis of hypertension[26,29]. This theory led to the inevitable question of whether a fundamental fault in these systems causes essential hypertension[30] — that is, whether a single cause of essential hypertension could be identified. However, essential hypertension is recognized to be a multifactorial disorder[31,32]. Almost certainly, several subtypes of essential hypertension will be identified, with different aetiologies and courses of development resulting from the interactions of multiple genes and environmental factors.

Computer modelling with parallel animal experiments has been used to examine the relative contributions of various factors involved in the control of tissue perfusion and blood pressure regulation[33–35]. These studies showed that healthy kidneys have an infinite capacity to normalize blood pressure in response to changes in salt and water intake and excretion. By contrast, diseased kidneys have impaired 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 noradrenaline spillover have provided direct evidence for sympathetic activation of 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 increases in 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 the SNS and the parasympathetic nervous system influence the activity of the heart, and the sympathetic component also acts on the vasculature. Portions of the

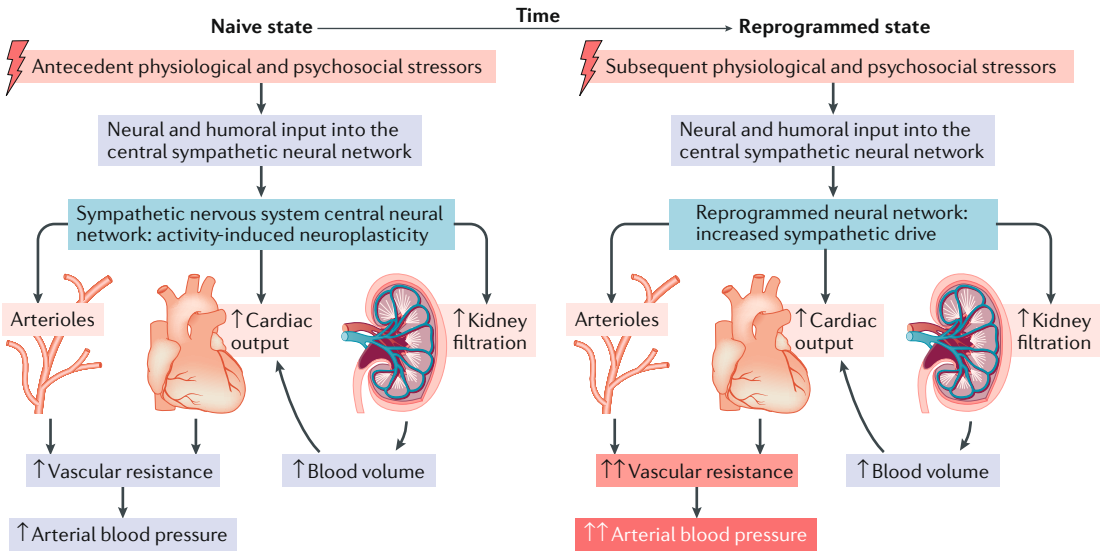


Fig. 1 | **The hypothetical role of neuroplasticity and hypertensive response sensitization in the aetiology and progression of essential hypertension.** In the stimulus-naive state, prior exposure to stressors activates the central neural network that controls sympathetic nervous system (SNS) tone and raises blood pressure. Over time, repeated exposure to stressors results in activity-driven neuroplasticity, which reprogrammes the central sympathetic neural network to increase sympathetic drive. In the reprogrammed state, sustained or new 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. If the increase in vascular resistance is sustained, vascular remodelling and chronic hypertension result.

Lamina terminalis
The single layer of ependymal cells that forms 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.

ANS are located in the periphery (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 can store information about prior SNS activations resulting from physiological and psychosocial stressors; the neural systems implicated in sympathetic responses to these two types of stressors share some, but not all, of their 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. These changes cause a corresponding change in afferent nerve signalling to the nucleus tractus solitarius, which triggers corrective reflexes. Humoral signals, by contrast, act on two forebrain regions that lack a blood–brain barrier: the subfornical organ and the organum vasculosum of the lamina terminalis (OVLT)[51]. The subfornical organ contains receptors for angiotensin II (ANGII), and the OVLT includes osmoreceptors that detect extracellular solute concentrations (mainly sodium). The subfornical organ and the OVLT, along with the median preoptic nucleus, process information relevant to the status of blood volume, pressure and extracellular fluid osmolality[52] (FIG. 2).

Hindbrain structures (the nucleus tractus solitarius and parabrachial nucleus) are connected to rostrally located structures in the hypothalamus and the amygdala and along the lamina terminalis (reviewed elsewhere[47–49,53]). The paraventricular nucleus is a key area in the hypothalamus that receives both ascending input from the hindbrain and descending input from the subfornical organ, OVLT and median preoptic nucleus. The paraventricular nucleus, therefore, functions as a key integrative node for processing information that is important for maintaining body fluid and cardiovascular homeostasis. Sympathetic premotor neurons projecting from the paraventricular nucleus innervate the intermediolateral cell column of the spinal cord either directly or indirectly via the rostral ventrolateral medulla. The

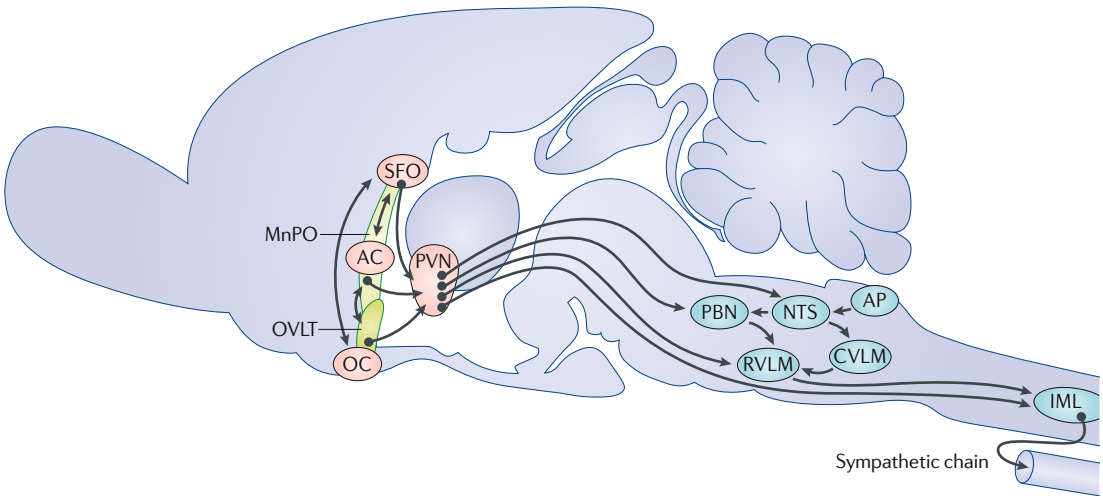


Fig. 2 | **A portion of the neural network controlling sympathetic tone and blood pressure.** The neural pathways arising from rostral structures located along the lamina terminalis and running caudally to the spinal cord are activated by physiological stressors indicating falls in blood volume and blood pressure. Structures located along the lamina terminalis, such as the subfornical organ (SFO), median preoptic nucleus (MnPO), organum vasculosum of the lamina terminalis (OVLT) and the paraventricular nucleus (PVN) of the hypothalamus, have been implicated in the neuroplasticity mediating sensitization of this hypertensive response. The SFO is the primary forebrain target for angiotensin II (ANGII), and cells in the OVLT function as osmoreceptors. The MnPO, which lies inside the blood–brain barrier, receives input from both the SFO and the OVLT and probably processes information about the status of intracellular and extracellular fluid compartments and blood pressure. The SFO, MnPO and OVLT 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 intermediolateral cell column (IML) of the spinal cord both directly and via the rostral ventrolateral medulla (RVLM). Also represented are some additional areas implicated in cardiovascular control: the area postrema (AP), caudal ventrolateral medulla (CVLM), nucleus tractus solitarius (NTS) and parabrachial nucleus (PBN), which all either directly or indirectly influence activity in the RVLM. AC, anterior commissure; OC, optic chiasm. Adapted with permission from REF.[116], American Physiological Society.

intermediolateral cell column 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 with the neural pathways that mediate 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. A 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 perifornical area in the lateral hypothalamus[55–58] and the dorsomedial hypothalamus have 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 intermediolateral cell column[49,53].

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 (ANGI), angiotensin-converting enzyme (ACE) and ANGII (reviewed elsewhere[62]). ANGII exerts its actions by binding to the type 1 and type 2 ANGII receptors (AT1 and AT2, respectively). Because ANGII is a major determinant of circulating aldosterone levels, and ANGII 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 ANGII to produce a heptapeptide, $ANG_{1–7}$, that binds to 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, anti-hypertensive) arm of the RAAS[62–64]. ANGII itself could also have both hypertensive and anti-hypertensive actions, as the effects of ANGII binding to AT2 oppose those produced by its binding to AT1 (REFS[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 other sites, including the vascular wall, heart, adipose tissue, haemopoietic bone marrow, lungs and 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 balance 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 the brain RAASs led to the proposal that circulating ANGII acts on the subfornical organ in an endocrine manner (that is, similarly to a circulating hormone) to activate ANGII-containing efferent neurons that use ANGII as a neurotransmitter or neuromodulator[72–74]. Substantial evidence continues to support this concept of humoral–neural coupling between the circulating and the brain RAASs (reviewed elsewhere[75]). In the brain, ANGII 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 subfornical organ and the intermediolateral cell column to increase SNS activity[75] (FIG. 2) and thereby induce activity-driven neuroplasticity.

Microglia, pro-inflammatory cytokines

Both neurons and brain glial cells participate in the control 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) signalling involved in immunomodulation. Levels of pro-inflammatory cytokines, including tumour necrosis factor (TNF), 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 show increased production of extracellular and intracellular reactive oxygen species[80–82]. Both spontaneously hypertensive rats and animals with ANGII-induced hypertension show microglial activation within the paraventricular nucleus, which is associated with increased levels of pro-inflammatory cytokines[80–82]. Blockade of brain microglial activation or targeted depletion of activated microglia within the paraventricular nucleus attenuates ANGII-induced hypertension, decreases pro-inflammatory cytokine levels within the paraventricular nucleus and reduces cardiac hypertrophy[81,82]. These results indicate that ANGII-induced microglial activation and the subsequent release of pro-inflammatory cytokines contribute to the development of hypertension. Of note, ANGII 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 subfornical organ to increase brain RAAS activity and inflammation[84–86]. This finding suggests that the sympathoexcitatory response to pro-inflammatory cytokines, which is mediated by the subfornical organ, depends on having an ambient level of activity of both the brain RAAS and pro-inflammatory cytokines[84–86].

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, which is in contrast to the tight coupling between neurons using synaptic neurotransmitters to communicate.

Cytokines
Proteins that are important in autocrine, paracrine and endocrine signalling, 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).

Plasticity in neural networks

In the late 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 elsewhere[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, can be induced at many other sites in the nervous system[90,91], including the sympathetic ganglia[92,93].

At the time when long-term potentiation 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 prior exposure to stressors can, through vascular and renal mediators, lead to increased systemic vascular resistance and high blood pressure (FIG. 1).

Hypertensive response sensitization

Our research group has investigated sensitization of the hypertensive response using an IND–DEL–EXP experimental paradigm[1] (BOX 1). In our initial experiments, either a very low (non-pressor) dose of ANGII or saline (vehicle) was administered during the induction phase. After a 1-week delay period, hypertension was elicited (the expression phase) by administering a slow-pressor dose of ANGII. Animals exposed to the non-pressor dose of ANGII during induction showed a sensitized hypertensive response during expression in comparison to rats that received vehicle during induction (BOX 1). A follow-up experiment demonstrated that the HTRS-inducing effects of ANGII were mediated by the CNS. Intracerebroventricular administration of non-pressor doses of ANGII 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 ANGII in the induction phase prevented HTRS[1].

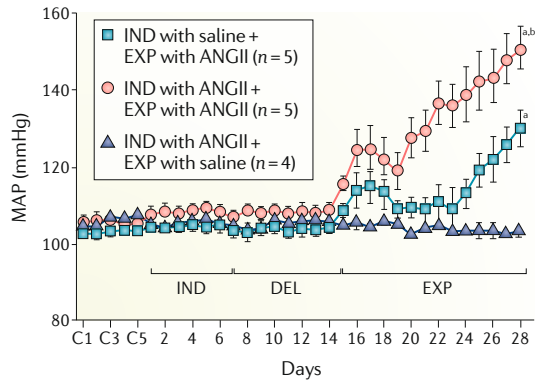
By employing the IND–DEL–EXP experimental design, it was possible to provide the first unambiguous demonstration that the hypertensive response can be sensitized[1]. The power of the IND–DEL–EXP method is that it disambiguates induction of a sensitized response from expression of sensitization. Most 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 reveals several phenomena that in all likelihood are examples of HTRS but were not interpreted as involving the processes of sensitization and CNS neuroplasticity. Two good examples of these phenomena are the induction of hypertension by prolonged systemic administration of very low doses of ANGII and the rapid expression of hypertension in animals exposed to renal artery clipping–unclipping and re-clipping, which are discussed below.

Large doses of ANGII administered systemically are well known to produce a rapid rise in blood pressure. However, in the mid-1960s, studies in rabbits demonstrated that continuous infusion of very low doses of ANGII that initially produced no notable rise in blood

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. The individual is then 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. The interval between induction and expression is termed the delay phase, which can range from no delay to many weeks.

The graph shown represents typical findings from an IND–DEL–EXP experiment showing hypertensive response sensitization (HTRS). 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 (ANGII) 10 ng/kg/min. The induction (IND) and delay (DEL) phases each lasted 1 week. Blood pressure changed little during the induction phase; a transient increase in blood pressure can occasionally be seen, which always returns to baseline before the start of the expression (EXP) phase. The delay phase enabled the persistence of the effects of HTRS induction to be assessed and any remaining exogenous ANGII to be metabolized. At the beginning of the expression phase, the rats received further treatment with either saline or a subcutaneous slow-pressor dose of ANGII 120 ng/kg/min. As this dose of ANGII does not immediately elicit hypertension, the initial rise in mean arterial blood pressure (MAP) seen in animals that received ANGII over the first 3–4 days of the expression phase probably represents the systemic vasoconstrictor action of ANGII. After 4 days, the vasoconstrictor effect of ANGII is replaced by increased sympathetic drive, which continues to increase blood pressure.



Data are expresse.d as means +/− standard errors. $^{a}P < 0.05$ versus baseline or versus induction with ANGII then expression with saline. $^{a,b}P < 0.05$ versus induction with saline then expression with ANGII.

pressure would, after several hours or days, produce frank hypertension[119,120]. This altered response occurred despite the fact that circulating levels of ANGII probably reached a steady state within a few minutes. This so-called slow-pressor effect of ANGII has been demonstrated in many species (including dogs[121], rats[122], mice[123], sheep[124] and humans[125]). This capacity of continuous administration of low doses of ANGII to progressively shift the dose–response curve upward and eventually produce an increase in blood pressure was originally termed angiotensin auto-potentiation[126,127]. Now, after recognizing that the hypertensive response can be sensitized, perhaps a more logical interpretation of this effect and a mechanistic clarification of the concept of auto-potentiation is that as the infusion of low-dose ANGII proceeds, a sensitized state is progressively induced that amplifies the ongoing rise in blood pressure.

Constriction of renal arteries, including with small metal clips, will induce hypertension after several days. In rats with established two-kidney, one-clip (2K-1C) renal hypertension, removal of the clip rapidly restores blood pressure to normal levels. However, re-clipping the renal artery a short time after clip removal very quickly re-establishes the hypertensive state[128,129]. This reinstatement of hypertension is much more rapid than the initial induction of hypertension by renal artery clipping. Also, shortly after the renal artery clip is removed (or the clipped kidney is ablated), pressor responses to exogenous renin or ANGII are substantially increased[128–130]. Notably, one unclipping–re-clipping experiment implicated the CNS in this mechanism by demonstrating that spinal cord destruction prevented the enhanced renin-induced pressor response in acutely unclipped 2K-1C rats[129]. Taken together, the results of clipping, unclipping and re-clipping studies indicate that the control of cardiovascular function behaved as though it recalled the condition induced by renal clipping. Because circulating renin levels are chronically increased in rats with 2K-1C renal hypertension[129], an initial rise in ANGII probably acted through neuroplasticity to reprogramme the CNS to trigger a sensitized hypertensive response to re-clipping of the renal artery or administration of exogenous renin or ANGII. Further investigations are needed to examine the nature of the central neuroplasticity associated with maintenance of the sensitized state in these phenomena.

Neuroplasticity

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 the delay and expression phases. Being able to collect tissue samples at the end of the delay phase is especially important because the blood pressure of the experimental group is then still normal and no 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 would be 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]. The most consistent observation has been upregulation of mRNA encoding AT1. This finding is compatible with many other in vivo and in vitro studies showing upregulation of AT1 or increased binding of ANGII to AT1 after treatments that elevate levels of ANGII[136–142] or after administration of a mineralocorticoid agonist[143–146]. These observations are particularly important because for most agonist–receptor interactions, increasing the concentration of a ligand typically downregulates its receptor. The functional importance of agonist-induced receptor upregulation in the RAAS is that it provides a feedforward mechanism of response amplification that could contribute to HTRS.

The recognition that very low doses of ANGII can sensitize the hypertensive response by reprogramming the CNS to make it more responsive to ANGII might

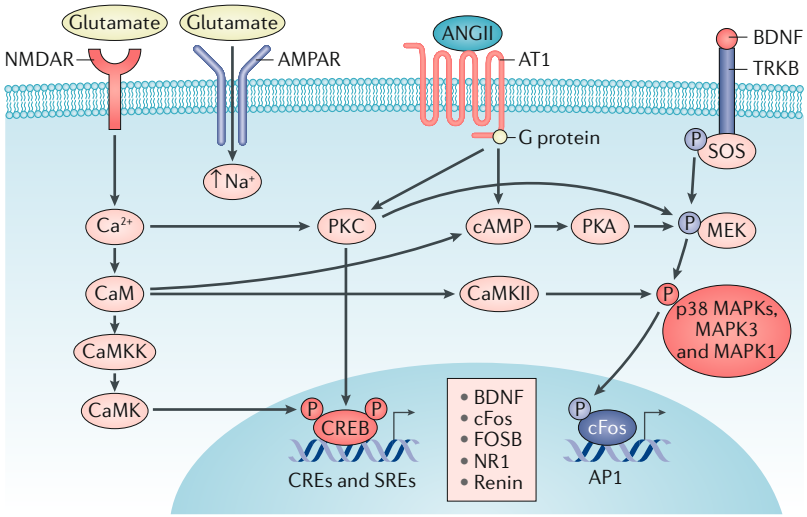


Fig. 3 | **Mechanisms involved in hypertensive response sensitization and neuroplasticity.** Many neural systems involve 'signature' neurotransmitters or neuromodulators. As some components of the hypertensive arm of the brain renin–angiotensin–aldosterone system (RAAS) are always upregulated after induction of hypertensive response sensitization (HTRS), the RAAS component ANGII might be considered a signature mediator in the neural pathways controlling sympathetic tone and blood pressure. Glutamate and glutamate receptors are involved in nearly all forms of neuroplasticity, and most cells in the nervous system express at least one type of glutamate receptor. Glutamate depolarizes neurons by binding to ionotropic *N*-methyl-D-aspartate receptors (NMDAR) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). Most, if not all, cells in the network controlling sympathetic tone have both NMDAR and AMPAR 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 inducing morphological changes. Brain-derived neurotrophic factor (BDNF) is associated with almost every aspect of neural and functional plasticity through its receptor TRKB. Finally, long-term neuroplastic changes involve protein synthesis, which requires activation of transcription factors, including AP1, c-Fos, FOSB and cAMP-responsive element-binding protein (CREB). Salmon-red colour indicates signalling mechanisms implicated in the neuroplasticity underlying HTRS. Future studies are needed to determine how many elements of the neural network controlling sympathetic tone and blood pressure manifest detectable changes and how long such changes persist. ANGII, angiotensin II; AT1, type 1 ANGII receptor; CRE, cAMP-responsive element; MAPK, mitogen-activated protein kinase; NR1, NMDAR subunit; SRE, serum responsive element. Adapted with permission from REF.[116], American Physiological Society.

help to explain the long-standing enigma observed in the treatment of many patients with essential hypertension — namely, why RAAS antagonists are successful in lowering blood pressure in some individuals with normal or low plasma renin activity[147,148]. It seems reasonable to speculate that in such patients, prior exposure to challenges might have induced HTRS, which was manifested by increased sensitization to ANGII or upregulated expression of AT1 in the CNS. Consequently, the capacity of RAAS antagonists to attenuate RAAS activity in the CNS would be increased, thereby reducing sympathetic tone and lowering blood pressure even in patients with normal or low plasma renin levels.

The study of the cellular and molecular basis of sensitization (a form of non-associative memory) has substantially advanced knowledge of the nature of the 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 is similar to that 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 ANGII or aldosterone given during induction of HTRS on growth factors in the lamina terminalis at the end of the delay phase, levels of brain-derived neurotrophic factor (BDNF) protein and *BDNF* mRNA were increased, whereas levels of vascular endothelial growth factor mRNA and protein remained unchanged[150]. Also, lamina terminalis tissues collected at the end of the delay phase showed no net increase in levels of the p38 mitogen-activated protein kinase (MAPK) family of second messengers nor the cAMP-responsive element-binding protein (CREB) family of transcription factors, although levels of the phosphorylated forms of these proteins increased significantly[150].

Collectively, the sustained changes in components of the RAAS observed at the end of the delay phase, along with other molecular indicators of synaptic plasticity, are consistent with the presence of neuroplasticity in the neural network controlling sympathetic tone and blood pressure (FIGS. 2,3). These changes are likely to represent memories of previously encountered hypertensive stimuli and to reflect the neural state underlying 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 ANGII interact cooperatively in the brain, indicating that both mechanisms must be intact for hypertension to occur in response to systemically administered ANGII 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 ANGII 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 that intracerebroventricular administration of aldosterone at a non-pressor dose during induction produced cross-sensitization when a slow-pressor dose of ANGII was delivered during the expression phase. Further evidence was provided by studies showing that intracerebroventricular administration of a mineralocorticoid receptor antagonist along with subcutaneous aldosterone during induction blocked HTRS[2].

Many different stressors cross-sensitize with ANGII 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. 1,3). 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, as provided below.

Table 1 | **Stimuli used to induce sensitization of the hypertensive response**

Stressor	Route of administration	Duration of challenge	Refs
Physiological stressor			
Non-pressor ANGII	Subcutaneous	1 week	1
Non-pressor ANGII	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	241
Lipopolysaccharide	Intraperitoneal	3 times in 1 week	Unpublished
Leptin	Intracerebroventricular	1 week	134
TNF	Intracerebroventricular	1 week	131
Psychosocial stressor			
Resident–intruder social defeat	External and/or psychosocial	3 times in 1 week	132,133
Perinatal challenges 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 (ANGII) 120 ng/kg/min in all studies. NA, not applicable; TNF, tumour necrosis factor.

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, 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 ANGII 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 ANGII, 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; 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 and IL-6 and a marker of microglial activation (CD11b)[131]. In parallel

Table 2 | **Treatments that block or reverse sensitization of the hypertensive response**

Blocking treatment	Route of administration	Sensitizing challenge	Refs
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 ANGII and intracerebroventricular leptin	131,134
Pentoxifylline	Intracerebroventricular	Blocks induction with high-fat diet, intracerebroventricular ANGII and intracerebroventricular leptin	131,134
AT1 antagonist	Intracerebroventricular	Blocks induction with high-fat diet, subcutaneous ANGII 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 ANGII in male rats and ovariectomized female rats	193
Raloxifene	Intracerebroventricular	Blocks induction with subcutaneous ANGII in male rats and ovariectomized female rats	Unpublished
Valproate	Subcutaneous	Blocks induction with subcutaneous ANGII	Unpublished
Sodium butyrate	Intraperitoneal	Blocks induction with subcutaneous ANGII	Unpublished
Dizocilpine (MK-801)	Subcutaneous	Blocks induction with subcutaneous ANGII	242
AP-5	Intracerebroventricular	Blocks induction with subcutaneous ANGII	242
$ANG_{1–7}$	Intracerebroventricular	Blocks induction with subcutaneous ANGII	193

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

experiments, animals fed a high-fat diet for 3 weeks were then returned to a normal diet and immediately challenged with a slow-pressor dose of ANGII, which evoked HTRS[131]. 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 feedforward 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, paraventricular nucleus, subfornical organ and hindbrain. Microinjection of leptin into the arcuate nucleus or paraventricular nucleus resulted in increased SNS activity[166,167], whereas deletion of the leptin receptor (LEPR) in the arcuate nucleus or subfornical organ 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]; these findings 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 subfornical organ and paraventricular nucleus[170]. These effects are ANGII-dependent, as some responses are reversed by deletion of AT1 in the paraventricular nucleus[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 intracerebroventricular administration of a LEPR antagonist prevented the induction of HTRS by 3 weeks of a high-fat diet[134]. Intracerebroventricular TNF was as effective in inducing HTRS as intracerebroventricular ANGII given at a non-pressor dose. TNF 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 synthesis or microglial activation blocked the induction of HTRS by either leptin or a 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 induction 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 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 overactivity 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 in not only the generation of increased basal blood pressure but also the development of enhanced renal sympathetic and pressor responses to physical stress, which are observed in the 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 subfornical organ 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 with the delay periods used in our early IND–DEL–EXP studies of HTRS. Consequently, prenatal studies have provided a good way to investigate the duration of the sensitized state that produces HTRS. Prenatal induction of HTRS was accomplished by subjecting pregnant dams to ANGII-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 ANGII 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 innate immune system within the brain) 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 drinking water 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 adult 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 were normalized in captopril-treated animals[191].

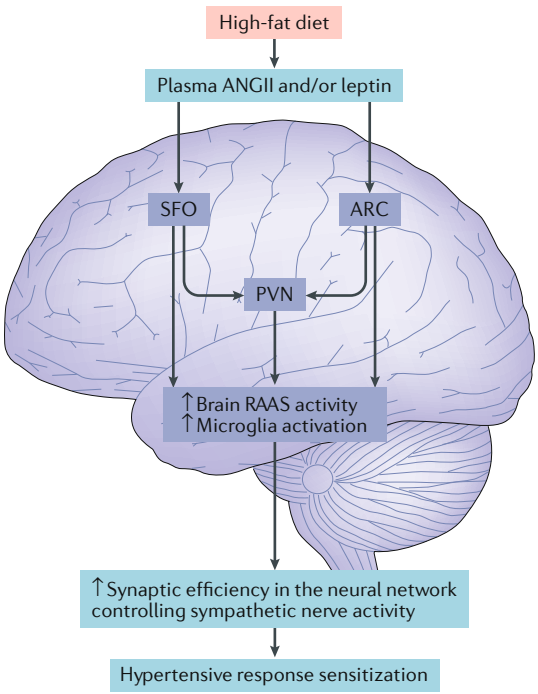


Fig. 4 | **How a high-fat diet and obesity might induce hypertensive response sensitization.** Both high-fat diet and obesity increase circulating levels of angiotensin II (ANGII) and leptin. Circulating ANGII and leptin act on the subfornical organ (SFO) and/or the hypothalamic arcuate nucleus (ARC), both of which have projections to the hypothalamic paraventricular nucleus (PVN). Actions of ANGII and leptin in the SFO, ARC and/or PVN activate the brain renin–angiotensin–aldosterone system (RAAS) and inflammatory mechanisms that induce sensitization by increasing synaptic efficiency in the SFO and/or PVN.

As noted above, many human and animal studies have found that female individuals (in comparison with their male offspring) are frequently protected from the adverse effects of experiences that would otherwise produce hypertension later in life. We have also seen that female animals are protected against the induction of HTRS[192,193]. Unfortunately, an in-depth discussion of the nature of the female sex-related protection against HTRS and the role of oestrogen and other anti-hypertensive factors prominent in female individuals is beyond the scope of this Review

In humans as well as in experimental animals, maternal obesity and maternal high dietary fat intake have adverse consequences for the health of the 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 offspring, have been studied in female rats fed a high-fat diet beginning 2 weeks before conception and continuing throughout both pregnancy and lactation, just during pregnancy or just during lactation[135]. The 10-week-old adult offspring of these rats, which initially had 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 ANGII or TNF[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 paraventricular nucleus in response to being challenged with a slow-pressor dose of ANGII during the expression phase[135].

The perinatal period has long been recognized as a critical time during which interventions are effective in reprogramming many physiological systems, particularly the nervous system[202,203]. 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 in the offspring. The resulting sensitized state, which predisposes these offspring to hypertension, is 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 stress[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 are 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 expression of mRNAs encoding AT1, IL-1β, IL-6 and TNF[132]. Pretreatment with captopril or administration of a TNF antagonist during the induction period abrogated the HTRS produced by resident–intruder pairings and blocked the increased expression of RAAS components and pro-inflammatory 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 both in human and in 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 approximately 51% of patients with hypertension and approximately 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 ANGII or aldosterone administration were studied in IND–DEL–EXP experiments to see whether 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 ANGII 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 ANGII 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 ANGII or aldosterone during a 1-week induction period[150].

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 ANGII. 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 sustained upregulation of the expression of RAAS components is of particular importance, as this feedforward 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 various environmental conditions[230]. In many physiological and behavioural systems, response sensitization is advantageous for defending the integrity of an organism 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, 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 savannah. Furthermore, under natural conditions, full recovery from severe hypovolaemia requires the acquisition of adequate amounts of water and sodium, which are 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 lifespan 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 (approximately 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 by not only challenges that produce hypovolaemia and blood pressure dyshomeostasis but also 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 RAASs might induce progressively greater and greater sensitization 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 a 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 prior events to the ongoing control of sympathetic tone and blood pressure.

One might be discouraged by realizing that stressor-induced insults are remembered 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 expression of HTRS (TABLE 2). As yet, few studies have used the IND–DEL–EXP paradigm to link changes in the neural control of the circulation to mechanisms involving sensitization of the hypertensive response; the work is in its infancy. The demonstration of the phenomenon of HTRS and the identification of some accompanying indicators of CNS neuroplasticity that enable the sensitized state to be maintained over extended durations raise many new questions that need to be answered, several of which are of particular relevance. What are the time 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 SNS to induce neuroplasticity and sensitization? What epigenetic changes are likely to maintain the sensitized state? How do dietary factors such as high intakes of fat or salt interact with the sensitized state to produce frank hypertension in the course of ageing? Are counter-regulatory mechanisms lost during ageing that buffer the sensitized state by preventing 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? Addressing these questions is expected to provide deeper insights into the causes, treatment and prevention of essential hypertension.

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