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Central regulation of stress-evoked peripheral immune responses

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Abstract

Stress-linked psychiatric disorders, including anxiety and major depressive disorder, are associated with systemic inflammation. Recent studies have reported stress-induced alterations in hematopoiesis that result in monocytosis, neutrophilia and lymphocytopenia and, consequently, upregulation of pro-inflammatory processes in immunologically-relevant peripheral tissues. There is now evidence that this peripheral inflammation contributes to the development of psychiatric symptoms, as well as to common co-morbidities of psychiatric disorders, such as metabolic syndrome and immunosuppression. Here, we review the specific brain and spinal regions, and the neuronal populations within them, that respond to stress and transmit signals to peripheral tissues via the autonomic nervous system or neuroendocrine pathways to influence immunological function. We comprehensively summarize studies that have employed retrograde tracing to define neurocircuits linking the brain to the bone marrow, spleen, gut, adipose tissue and liver. Moreover, we highlight studies that have used chemogenetic or optogenetic manipulation, or intracerebroventricular administration of peptide hormones, to control somatic immune responses. Collectively, this growing body of literature illustrates potential mechanisms through which stress signals are conveyed from the CNS to immune cells to regulate stress-relevant behaviours and co-morbid pathophysiology.

Introduction

In the 17th century, Descartes proposed the theory of interactionism — a philosophical belief positing that the mind and body were separate and distinct entities that could influence each other. Contemporary neuroscientists now have a growing understanding that psychological states can indeed impact physiological processes in the periphery, such as metabolism, host defense and cardiovascular function[1]. In turn, somatic states are sensed by the CNS to shape

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and guide behaviour[2]. Underlying many of these processes are cells of the immune system, which have diverse inflammatory and regulatory roles and are embedded in all tissues throughout the body. The emerging field of neuroimmunology investigates how neurons, leukocytes and their signaling molecules interact in homeostatic and pathological situations. While central control of autonomic functions, such as respiration and digestion, has been extensively studied, the specific neuronal populations involved in top-down brain-to-body circuits regulating systemic immune responses are less well understood.

Here, we review the current literature to discuss how a negative affective state brought upon by psychological stress can control peripheral immunity. Specifically, we highlight stress-responsive brain regions that innervate immunologically-relevant tissues, such as the bone marrow, spleen, gastrointestinal tract, adipose tissue and liver, largely through the autonomic nervous system and hypothalamic–pituitary–adrenal (HPA) axis. In addition, we address how immune cells in these tissues respond to stress and how these responses contribute to physiological and behavioural changes associated with stress-relevant psychiatric disorders, such as anxiety and depressive disorders. These studies reveal a feedback loop between the nervous and immune systems that becomes hijacked during chronic stress to propagate psychiatric illness and inflammatory co-morbidities.

Linking chronic stress and inflammation

According to the latest estimate from the Global Burden of Disease Study, anxiety and depressive disorders each affect approximately 300 million people worldwide[3]. These highly prevalent disorders represent some of the most debilitating conditions, accounting for 60% of the over 125 million disability-adjusted life years (DALYs) resulting from mental disorders[3]. It is becoming increasingly recognized that individuals with stress-related disorders, such as major depressive disorder (MDD), exhibit signs of chronic low-grade systemic inflammation. These include elevated pro-inflammatory cytokines in serum, dysregulated myelopoiesis and lymphopoiesis, and disruption of body barriers including the gut epithelium and blood-brain barrier (BBB)[4–8].

Unsurprisingly, people with MDD display high rates of co-morbidity with immune and inflammatory conditions, such as rheumatoid arthritis, cardiovascular disease, metabolic syndrome and inflammatory bowel disease (IBD)[9–12]. A pivotal study in 1987 reported that a subpopulation of people with viral hepatitis treated with interferon (IFN) α — a pro-inflammatory anti-viral cytokine[13] — developed depression[14], demonstrating that a pro-inflammatory molecule in the periphery could directly influence mood. Consistent with this finding, individuals with prior hospitalizations for infections or autoimmune diseases display greater odds of subsequently developing depression, with multiple infections having additive effects[15]. It is important to note, however, that lifestyle factors (such as pain arising from rheumatoid arthritis or social isolation during SARS-CoV-2 infection) can contribute to or exacerbate depressive symptoms[16,17]. Perpetuating this cycle, there is evidence that depression compromises the immune system and heightens the risk of infection[18,19]. However, the cellular and molecular mechanisms underlying this bi-directional relationship between the brain and body that regulates the pathogenesis of both psychiatric and inflammatory conditions requires further interrogation. Ongoing questions

include whether psychological stress can directly influence systemic inflammation, how the brain communicates with peripheral tissues (including the immune system), what tissue-specific immune responses are evoked by stress and how peripheral inflammation or immune dysregulation is detected by the CNS to elicit behavioural changes.

To address the first of these questions, numerous studies have measured circulating cytokine concentrations in individuals with MDD or anxiety, diagnosed using criteria set by the Diagnostic and Statistical Manual of Mental Disorders (DSM)[20]. Circulating pro-inflammatory cytokines, including interleukin-1α (IL1A), IL1B, IL2, IL6, IL8, IL12, IFNγ (also known as IFNG), and tumour necrosis factor α (TNF), as well as chemokines, such as C-C motif chemokine 2 (CCL2), CCL3, CCL11, C-X-C motif chemokine 4 (CXCL4), CXCL7 and CXCL8, are reportedly increased in individuals with MDD compared to control subjects[21–25]. These cytokine and chemokine concentrations are often sharply increased at the time that the individual is exposed to a stressor, then diminish with time from the precipitating stressful event(s). For example, plasma IL6 levels increase following the Trier social stress test and this increase is greater in subjects with MDD than in healthy control subjects[26]. Interestingly, serum cytokine profiles in people with MDD show considerable overlap with those seen in people with common co-morbid inflammatory disorders, including IBD, metabolic syndrome and coronary artery disease, although often the concentrations are lower in magnitude (Table 1).

While these findings support an association between MDD and anxiety with peripheral inflammation, analyses of human populations are largely correlative and cannot conclusively define causal directionality. Therefore, animal models of stress, including chronic variable stress (CVS) and chronic social defeat stress (CSDS), which recapitulate biological and behavioural phenotypes associated with anxiety and depression, are invaluable tools to uncover how the stressed brain communicates with the peripheral immune system (Box 1). Similar to people with MDD, a subset of rodents exposed to CVS or CSDS also have higher levels of pro-inflammatory cytokines and chemokines, such as IL1A, IL1B, IL6, IL12, TNF, CCL2, and CCL5, in the bloodstream compared to unstressed control mice and stress-resilient mice (mice that do not develop social avoidance behaviour or deficits in reward-related behaviours despite being exposed to similar levels of stress)[25,27–30]. This suggests that peripheral inflammation is a direct consequence of psychosocial stress in a subset of vulnerable mice. Moreover, animals that are exposed to chronic stress are predisposed to the development of inflammatory conditions, such as experimental autoimmune encephalitis, colitis, atherosclerosis and diabetes[31–34]. Thus, the experience of psychological stress — independent from any prior or concurrent immune challenge — exerts whole-body immunomodulatory activity, provoking inflammation and vulnerability to inflammatory disease. Using these animal models of stress, several studies have begun to unravel how peripheral immunity could be centrally regulated.

Brain-to-bone marrow neurocircuits

One possible way that psychological states may be linked to somatic symptoms, such as inflammation, is through the direct innervation of peripheral tissues by the CNS (via the peripheral nerves). Early work identified autonomic innervation of immune organs,

including the bone marrow, which contains haematopoietic stem cells that give rise to all blood cells including monocytes, neutrophils, and lymphocytes, thereby laying the foundation for future investigates of brain-to-body communication[35]. Polysynaptic retrograde viral tracing from immune-relevant organs in animals has become an important tool for deciphering these anatomical pathways in greater detail. Most commonly, pseudorabies viruses (PRVs) expressing reporter genes have been used for this purpose, as they exhibit rapid trans-synaptic propagation (crossing approximately one synapse every 24 hours after infection)[36]. Employing this strategy, the authors of one study injected the PRV Bartha strain (which only undergoes retrograde synaptic transmission) expressing the gene encoding green fluorescent protein (GFP) into the femoral bone marrow of male Wistar rats and then collected brain and spinal cord tissue to identify regions that innervate the bone marrow[37]. They found GFP in sympathetic chain ganglia at the lumbar level of the spine and in the intermediolateral cell column of the thoracic spinal cord, as well as in the ventrolateral medulla, four days after infection[37]. By five days after infection, PRV was detected in all regions of the spinal cord examined, along with the medulla, including the nucleus of the solitary tract (NTS), gigantocellular reticular nucleus (Gi), lateral paragigantocellular nucleus (LPGi), raphe pallidus nucleus (RPa), as well as in the ventral tegmental area (VTA), periaqueductal grey (PAG), locus coeruleus (LC), paraventricular nucleus of the hypothalamus (PVH), and lateral nucleus of the hypothalamus (LH)[37]. Six days after PRV infection, the virus had spread to regions including the bed nucleus of the stria terminalis (BNST), arcuate nucleus of the hypothalamus (ARH), amygdala, hippocampus, insular cortex, septum and motor cortex[37]. Of note, similar CNS regions were identified using PRV tracing from bone marrow in mice[38], suggesting that these neurocircuits are conserved across species. Regions detected by retrograde tracing from the bone marrow are summarized in Fig. 1.

Notably, several of these bone marrow-innervating brain regions have been implicated in stress responses, reward processing and the pathogenesis of depression and anxiety disorders. For example, dopaminergic projections from the VTA to the nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala and hippocampus that regulate responses to rewarding or aversive stimuli are reportedly dysregulated in people with MDD as well as in rodent models of chronic stress[39–42]. Moreover, stress activates neurons in the lateral septum to blunt social reward in susceptible mice[43], whereas it activates LC neurons in resilient mice to promote resilience to social avoidance behaviour[44–46]. Similarly, regions of the hypothalamus, including the PVH, LH and ARH, are activated by chronic stress in rodents[47–51], with the PVH being a key component of the HPA axis that can also coordinate stress responses through neuroendocrine mechanisms[52]. Other stress-sensitive brain regions that project to the bone marrow, such as the BNST and central amygdala (CeA), also integrate emotional signals and activate the HPA axis to promote anxiety or fear responses[53–55]. However, whether these brain regions can affect immunological function in the bone marrow remains a topic for future exploration.

MDD in humans and chronic stress in rodents are associated with monocytosis, neutrophilia and lymphocytopenia, which can be attributed to altered proliferation of hematopoietic stem cell (HSC) subpopulations or mobilization of leukocytes from the bone marrow[33,56–58]. Specifically, mice exposed to either CVS or CSDS exhibit an expansion of myeloid

progenitor cells, along with a downregulation of lymphoid progenitors[33,59]. It is well established that bone marrow receives dense sympathetic innervation, which contributes to the mobilization of leukocytes into circulation during stress or under homeostatic conditions[60,61]. Mechanistically, it has been shown that signaling by noradrenaline released by these sympathetic fibres within the bone marrow niche suppresses expression of CXCL12[33], which normally inhibits haematopoiesis and retains neutrophils and monocytes within the bone marrow[62–64]. Furthermore, it has been reported that repeated social defeat decreases CXCL12 expression in the bone marrow, thereby increasing monocyte release from the bone marrow, in a mechanism blocked by adrenalectomy or by treatment with metyrapone, a corticosterone synthesis inhibitor[65]. As neurons in the PVH and LC project to sympathetic centres in the brain stem and spinal cord, it is possible that elevated sympathetic tone arising from the activation of these brain regions during chronic stress drives these HSC and leukocyte dynamics in the bone marrow[66–68]. To determine if stress-regulated leukocyte mobilization was centrally regulated, one recent study used chemogenetics to regulate the activity of specific neuronal populations throughout various brain regions and then assessed circulating immune cell numbers[69]. The authors found that stimulating corticotropin-releasing hormone-expressing (CRH^+) neurons in the PVH, which increases plasma corticosterone concentrations, leads to the retention of T cells, B cells and monocytes in the bone marrow, thereby reducing their numbers in circulation; conversely ablating CRH expression in the PVH prevented the decrease in T cells, B cells, and monocytes in the blood following acute restraint stress, as did inhibiting CXCR4, the receptor for CXCL12[69]. Further, this effect was found to be HPA axis-dependent, as adrenalectomy prevented these changes[69]. Although the effects of PVH neuron stimulation on monocyte retention by the bone marrow may seem to contradict those expected from studies of chronic stress, it is likely that these differences may arise from differences in monocyte mobilization dynamics during acute stress or HPA axis activation, compared to chronic stress[70]. Interestingly, acute restraint stress was also shown to induce neutrophilia and this was found to be regulated by different brain regions than those regulating monocyte and lymphocyte mobilization. Stimulation of the motor cortex or medulla using optogenetics led to skeletal muscle expression of CXCL1, a chemokine for neutrophils[71], while ablating or inhibiting these regions ameliorated the restraint stress-induced neutrophilia[69]. Additionally, chemogenetic activation of dopaminergic neurons in the VTA, which encode reward behaviour, increased circulating B cell numbers[72]. These effects were found to be mediated in part by the sympathetic nervous system, as 6-hydroxydopamine (6-OHDA) treatment to ablate sympathetic neurons in the periphery prevented the peripheral immune responses[72]. It is important to note that while chemogenetic and optogenetic tools have been impactful in uncovering CNS regulation of peripheral immunity, they do not perfectly emulate physiological neuronal activation during stress or the complex signaling that arises from multiple distinct populations of neurons. Nevertheless, these studies demonstrate the capability of brain activity to regulate leukocyte production, retention and egress from the bone marrow under stressful conditions via the HPA axis, autonomic nervous system and actions of peripheral chemokines (Fig. 2). Additional studies are needed to further elucidate the upstream circuits involved in these processes, as well as to disentangle how myelopoiesis and monocytosis are regulated by the CNS.

There is a growing body of literature implicating monocytosis, neutrophilia and dysregulation of hematopoiesis in the manifestation of depression or anxiety-related behaviours following stress in rodents, thus providing a possible link between chronic stress and mood disorders. When HSCs from the bone marrow of stress-susceptible mice are transplanted into naïve mice, for example, the recipient mice become socially averse following a subthreshold social defeat that normally does not confer depressive-like behaviour[25]. This altered behaviour is hypothesized to result from increased recruitment of inflammatory leukocytes to reward centres in the brain (such as the NAc) in stressed individuals or animals and from the greater capacity of their to produce pro-inflammatory cytokines, such as IL6 and TNF. Consequently, these cytokines can directly induce depressive-like behaviours (including social avoidance, reduced sucrose preference and immobility in the forced swim test)[25,73]. Mechanistically, social defeat stress upregulates inflammatory TNF and/or nuclear factor-κB (NFKB) signaling pathways in endothelial cells and diminishes expression of the tight junction protein claudin-5 (CLDN5)[7,74]. This allows pro-inflammatory leukocytes, or their secreted factors (such as IL6 or matrix metalloproteinase-8), to enter the brain parenchyma where they impact neuronal excitability[7,75,76] (Fig. 3). For further details about the connections between peripheral immunity and depression, including mechanisms affecting leukocyte migration, BBB permeability, neurogenesis and synaptic transmission we refer the reader to REF[6].

Brain-to-spleen and -gut neurocircuits

Another major lymphoid organ responsible for chronic stress-evoked monocytosis is the spleen and many studies have recognized its involvement in inflammatory responses to psychological stress. Chronic social stress in mice leads to splenomegaly, attributed to granulocyte accumulation and ectopic (or ‘extramedullary’) myelopoiesis, which consequently elevates circulating monocyte levels[59,77]. In addition, the spleen is a major site of the germinal centre reaction, in which antigen-specific antibody-producing plasma cells undergo clonal expansion[78]. Recently, the brain–spleen axis has gained attention for its role as a direct neural pathway through which cognition and emotion can control peripheral immunity during stress[79]. To identify the brain regions that innervate the spleen, several groups have injected PRVs into the spleens of rats and mice[80,81]. In these experiments, PRV was detected in the thoracic spinal nucleus two days after infection and then, after three days, in stress-related brain and brain stem regions — including the PVH, LH, NTS and the dorsal motor nucleus of the vagus (DMV)[80,81]. By four days post-infection, PRV was found in the CeA, BNST, LC, lateral septum, insular cortex, motor cortex, ARH and the dorsomedial nucleus of the hypothalamus (DMH)[80,81]. These data indicate that there is considerable overlap between stress-responsive CNS regions that innervate the spleen and bone marrow (Fig. 1), with bifurcating signals from these regions giving rise to distinct immunophenotypes in these tissues.

Of the spleen-innervating brain regions, the PVH and CeA are among those with the most projections to the splenic nerve. It was shown that optogenetic stimulation of CRH^+ neurons in both the PVH and CeA is sufficient to increase the firing rate of the splenic nerve, indicating that CRH^+ neurons are functionally connected to the spleen[80]. These connections were proven to be immunologically relevant as splenic plasma cell formation was promoted

by their chemogenetic activation and diminished by their inhibition or ablation[80]. The authors speculated that this CNS control of plasma cell expansion was dependent on direct innervation, rather than neuroendocrine mechanisms, because splenic denervation disrupted the brain–spleen connection, and glucocorticoids produced by the HPA axis lowered plasma cell numbers[82]. To illustrate the ethological relevance of this circuit, mice were exposed to mild acrophobic stress, which activated CRH^+ neurons in the PVH and CeA and heightened plasma cell production, an effect that was abrogated by splenic denervation[80].

Another recent study explored the link between the DMV and spleen, demonstrating that optogenetic stimulation of neurons in the DMV triggers action potentials in the splenic nerve and inhibits endotoxin-induced production of the pro-inflammatory cytokine TNF[83]. As neurons within the DMV drive parasympathetic functions in peripheral tissues[84], this suggests that parasympathetic activity has anti-inflammatory roles in the spleen, while sympathetic inputs have known inflammatory functions[85]. Moreover, as both the PVH and CeA provide inputs to the DMV[86,87], it is possible that the DMV integrates signals from stress-responsive brain regions to coordinate peripheral immune responses. Interestingly, there are also reported anti-inflammatory effects of stress on the spleen, with restraint stress initiating a cholinergic pathway via the sympathetic nervous system that activates an anti-inflammatory program in splenocytes that protects against ischemia-reperfusion injury in mice[88]. This mechanism was re-capitulated by optogenetically activating tyrosine hydroxylase-expressing (TH^+) C1 neurons in the medulla[88]. In the spleen, there is evidence that vagus nerve stimulation triggers neurons in the splenic nerve to release noradrenaline, which is detected by the β2-adrenergic receptor on splenic choline acetyltransferase-expressing $(ChAT)^+$ T cells[89]. Consequently, these T cells produce acetylcholine, which suppresses pro-inflammatory cytokine production by splenic macrophages via the α7 nicotinic acetylcholine receptor[89]. Stress-activated brain–spleen circuits involved in splenic immune function are summarized in Fig. 2.

With constant exposure to pathogenic and food-related antigens and as the home of many lymphoid follicles, the gastrointestinal tract represents another immunologically relevant tissue that is sensitive to stress. Substantial research has investigated the communication between the central and enteric nervous systems (also known as the gut–brain axis) and its impact on local and systemic inflammation. First, a number of groups have employed PRV retrograde tracing to identify brain regions innervating different regions of the intestines (Fig. 1). In one study, PRV was detected in spinal cord neurons three days following injection into the rectum of rats and by four days, it was located in brain stem regions (including the NTS, LC, DMV, PAG, RPa, Gi, and parabrachial nucleus (PB))[90]. In a separate report, four days after a PRV expressing red fluorescent protein (RFP) was injected into the ileum, RFP-positive cells were also found in the NTS, DMV, RPa, and Gi[91]. Thus, different segments of the gastrointestinal tract may receive inputs from common CNS regions. Another recent study collected brain samples five days following infection of the duodenum with a PRV expressing GFP, and observed GFP in similar brain stem regions (including the NTS, LC, DMV, RPa, PBN, and Gi), but also in brain regions such as the LH, PVH, BNST, CeA, insular cortex and motor cortex[92]. Of note, several of these gut-innervating brain stem regions are also active during stress[93].

Growing evidence suggests that chronic stress impairs healthy gastrointestinal function, presenting as dysregulated intestinal motility, dysbiosis of the microbiota and initiation of low-grade inflammation[94,95]. These symptoms are common features of IBS, for which stress is a major risk factor[96]. Stress has also been shown to exacerbate symptoms of experimental colitis in rodents, with some evidence that this is centrally regulated. For example, one study reported that chronic water avoidance and restraint stress amplified histological damage and myeloperoxidase (MPO) activity in the colon in response to 2,4,6-trinitrobenzenesulphonic acid (TNB), which was used to induce colitis in rodents[97]. Moreover, intracerebroventricular injections of CRH (which is produced by cells in the PVH and CeA and can induce freezing behaviour[98]) was found to aggravate colitis symptoms triggered by TNB and stress, while the CRH antagonist astressin reduced these symptoms[97]. Similarly, intracisternal injection of orexin (which is largely produced by cells in the LH) can prevent ethanol-induced gastric mucosal damage[99]. Mechanistically, a recent study reported that chronic restraint stress aggravates dextran sulfate sodium (DSS)-induced colitis in a pathway that is dependent on the HPA axis. The authors found that enteric glia upregulate colony stimulating factor 1 (CSF1) in response to glucocorticoids generated as a result of stress and that this consequently promotes colitis by inducing TNF production by colonic monocytes[100]. While these studies demonstrate that gastrointestinal inflammation and homeostasis can be modulated by the CNS, they do not directly demonstrate the specific cells within the brain that regulate these processes.

Interestingly, a recent study demonstrated a bi-directional gut–brain circuit linking the insular cortex to colon inflammation[101]. Using *Fos*^{TRAP} mice, which allow specific labeling of active neurons, the authors identified a population of neurons in the insular cortex activated by DSS-induced colitis. After a recovery period, these neurons were then re-activated using chemogenetics. This recapitulated aspects of the colonic inflammation, such as increased intraepithelial and lamina propria leukocytes, greater activation of intraepithelial γδT cells, CD4-expressing (CD4$^+$) T cells, and CD8$^+$ T cells, and elevated IL6 and TNF expression by CD4$^+$ T cells and monocytes, respectively[101]. Importantly, activation of these neurons in the absence of prior DSS challenge did not exert any inflammatory effects in the colon, suggesting that the insular cortex neurons connected to the gut can encode an immunological memory of a peripheral inflammatory state[101]. However, broad non-specific chemogenetic inhibition of insular cortex neurons during DSS administration prevents colitis, implying that non-specific inhibition of insular cortex activity can directly alleviate peripheral inflammation in the gut[101]. Lastly, the authors applied the same strategy to label insular cortex neurons activated by zymosan-induced peritonitis and found that re-activation of these neurons could trigger inflammation in the peritoneal cavity, but not the colon, demonstrating tissue specificity in the centrally-encoded immune memory[101]. This study exemplifies how one brain region can regulate immunity in different peripheral tissues depending on context and prior environmental cues. Within the gut, the efferent signals relayed by the CNS are received by the enteric nervous system, which is composed of a vast and diverse number of neuronal subpopulations, glia and extrinsic ganglia. Growing data suggest that the enteric nervous system influences intestinal immunity. For example, activation of type 2 innate lymphoid cells (ILC2) in the gut mucosa is regulated by neuronally-derived peptides, with neuromedin U initiating[102], and α-

calcitonin gene-related peptide (αCGRP) antagonizing, type 2 immunity[103]. Additionally, it was reported that serotonin exacerbates, while oxytocin inhibits, proinflammatory cytokine expression in a mouse model of necrotizing enterocolitis[104]. Further in-depth discussion of the mechanisms by which the peripheral nervous system regulates inflammation and immunity in various tissues, including the gut, are reviewed in REF[105]. More work is needed to identify specific enteric nervous system cells that become activated or dysregulated by chronic stress.

There is also evidence indicating that gut inflammation can contribute to stress-relevant behaviours. One recent study showed that CSDS in mice promotes differentiation of IL17-expressing γδ T cells in the colon, in a process that is dependent on dectin-1 signaling[95]. When these cells were neutralized or dectin-1 was genetically knocked out, mice were protected against CSDS-induced social avoidance[95]. Therefore, it is possible that stress signals in the CNS are transmitted to the gut where they initiate inflammation that consequently influences behaviour (Fig. 2). Mechanistically, inflammatory intestinal leukocytes, including $IL17^+$ T cells as well as mast cells, may contribute to the breakdown of the intestinal epithelial barrier and the accompanying downregulation of tight junction proteins CLDN5, occludin (OCLN) and tight junction protein 2 (ZO-2)[106,107]. This may contribute to the MDD-associated elevations in circulating bacteria-derived compounds (such as lipopolysaccharide (LPS)[108]), which is recognized by toll-like receptor 4 (TLR4) on peripheral blood mononuclear cells (PBMCs) that trigger pro-inflammatory cytokine production[109]. Notably, PBMCs isolated from people with MDD exhibit greater TLR4 expression and responses to TLR4 stimulation[110,111]; thus, stress-induced endotoxemia may contribute to systemic inflammation that impinges on behaviour (Fig. 3). Importantly, however, additional studies are required to dissect the precise pathways through which the brain communicates with specific gut immune cell subpopulations.

Brain regulation of immunometabolism

Metabolic dysfunction is another common consequence of chronic stress in both humans and animals, with significant co-morbidity existing between MDD and metabolic syndrome[112]. Moreover, metabolic inflammation — leukocyte infiltration and pro-inflammatory signaling in insulin-responsive tissues — promotes systemic hyperglycemia[113]. Thus, it is conceivable that central responses to stress contribute to inflammatory processes implicated in glucose metabolism, in addition to behavioural outcomes.

One of the most widely analyzed tissues in the field of metabolic inflammation is the visceral adipose tissue. It plays a major role in energy expenditure, glucose handling and adipokine production and is considered an immunologically active organ due to the rich numbers of immune cells residing in the its stromal vascular fraction (SVF)[114]. In conditions under which metabolic inflammation arises, such as obesity or high fat feeding, there is an accumulation of pro-inflammatory macrophages, neutrophils, mast cells, type 1 innate lymphoid cells (ILC1s), B cells and Th1 T cells in the adipose tissue, and a concomitant decrease in alternatively-activated macrophages, eosinophils, ILC2s and regulatory T cells (Tregs)[115–124]. This is accompanied by expression of pro-inflammatory cytokines and

chemokines including CCL2, IL6 and TNF[125], conferring whole-body glucose intolerance. Notably, chronic stress synergizes with high fat feeding in mice to exacerbate insulin insensitivity, as well as adipose tissue inflammation[126]. As the adipose tissue is densely innervated by sympathetic nerves, several studies have reported the involvement of the peripheral nervous system in adipose tissue inflammation[127]; however, comparatively less is known about how the CNS regulates leukocyte infiltration and inflammatory polarization in metabolically-relevant tissues.

Taking advantage of PRV tracing, a number of groups have identified efferent neural circuits from the CNS to adipose tissue (Fig. 1). Three days after PRV injection into the retroperitoneal adipose depot in rats, retrograde viral transport is visible in thoracic intermediolateral spinal nuclei and sympathetic preganglionic spinal neurons[128]. At this time point, PRV is undetectable in hindbrain and forebrain regions. However, by four days post-viral inoculation, PRV is identified in brain stem regions including the LC, rostral ventromedial medulla (RVM) and midline raphe, as well as hypothalamic regions, including the PVH and LH[128]. After five days, PRV infection is widespread throughout the brain, becoming abundant in the NTS, RPa, PAG, ARH, BNST, amygdala, insular cortex and motor cortex, among others[128]. Consistent with these findings, PRV injected into gonadal fat pads of mice could be detected in the PVH and LH within 3–4 days of infection, and then in the PAG, Gi, NTS, RPa and LC after four days[129]. In this study, PRV appeared in the DMV, CeA, ventromedial nucleus of the hypothalamus (VMH), ARH and lateral septum after five days and then reached the BNST by six days post-infection[129]. Of note, injecting PRV into adipose tissue exclusively on the right side of the abdominal cavity yields bilateral labeling of brain stem and brain neurons[128]. Interestingly, one group found that male rats injected with PRV in the retroperitoneal adipose tissue had greater numbers of PRV^+ neurons in most analyzed regions, including the NTS, RPa, PVH and LH, compared to those in female rats[128].

Using laser capture microscopy to characterize adipose-projecting neurons, approximately 30–40% of PRV^+ neurons in the ARH were found to express the anorexigenic prohormone proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART), but not the orexigenic agouti-related peptide (AGRP) or neuropeptide Y (NPY)[128]. Additionally, LH neurons innervating the retroperitoneal adipose tissue were identified to express orexin and melanin-concentrating hormone (MCH)[128]. In separate studies in which PRV was injected into epididymal white adipose tissue of mice or Siberian hamsters, the authors found that significant numbers of PRV^+ neurons in the PVH also contained CRH, oxytocin, vasopressin (AVP) or pro-thyrotropin-releasing hormone (TRH)[129,130]. Further, PRV co-localized with NPY^+ neurons in the NTS[129]. These findings highlight specific neuronal populations that may regulate adipose tissue physiology, including inflammation.

Few studies have investigated the direct actions of the CNS on adipose tissue inflammation. Direct intracerebroventricular injections of AGRP reportedly increases TNF expression in epididymal white adipose tissue by suppressing sympathetic nerve activity[131]. While this suggests that a direct neural pathway connects the brain to adipose inflammation, it is also possible that central actions of feeding hormones, such as AGRP and POMC, could influence peripheral inflammation via effects on food intake behaviour, as hyperphagia also

causes adipose tissue expansion and immune cell infiltration[132]. One recent study defined a brain–adipose circuit that controls ILC2 function in adipose tissue[133]. First, retrograde tracing confirmed innervation of the gonadal adipose tissue by the PVH. The authors then introduced electrolytic lesions bilaterally in the PVH to ablate its function, which caused a significant reduction in adipose tissue ILC2s[133]. Importantly, the presence of adipose ILC2s and their corresponding type 2 cytokines, such as IL5 and IL13, was associated with decreased weight gain after high fat feeding and improved glucose tolerance[133]. This implies that PVH activity may in part normalize systemic glucose homeostasis via a mechanism mediated by adipose tissue ILC2s (Fig. 2). However, as this study non-specifically ablated a heterogeneous population of PVH neurons, further research is required to determine which neuronal subsets can regulate adipose tissue inflammation.

In addition to adipose tissue, the liver plays a critical role in stress-elicited metabolic abnormalities, with chronic foot shock and restraint stress inhibiting glycogenesis and upregulating hepatic gluconeogenesis[134]. Both chronic stress and metabolic syndrome have also been associated with hepatic steatosis and markers of liver inflammation, such as macrophage infiltration and expression of pro-inflammatory cytokines and chemokines (including IL6, TNF and CCL2)[135–138]. Since pro-inflammatory polarization of immune cells in the liver directly leads to insulin resistance[138], a brain–liver axis may link chronic stress to hyperglycemia via hepatic inflammation.

PRV tracing from the liver has revealed brain regions that innervate the liver and therefore may be involved in centrally-regulated hepatic inflammation (Fig. 1). The time course of one study involved collecting spine and brain tissue 3 – 7 days after PRV injection into the liver of mice[129]. After three days, PRV was only detectable in the spinal cord; however, by four days, it was found in the DMV, Gi, and PVH. Five days following PRV injection, neurons in the LC, PAG, NTS, VTA and LH, among others, were infected. After six days, PRV had migrated to additional stress-relevant brain regions, including the RPa, ARH, CeA, VMH and BNST, and then to the cortex after seven days[129]. A tracing experiment performed in rats by a separate group confirmed that the DMV projects to the liver and that, interestingly, hepatic sympathetic denervation prevents PRV from traveling from the liver to the brain. This suggests that brain–liver innervation is dependent on the sympathetic nervous system[139]; however, the liver also receives parasympathetic innervation via the vagus nerve[140].

Immunohistochemical analyses have revealed that PVH neurons that innervate the liver express CRH and oxytocin, but not AVP or pro-TRH[129]. Similar to the adipose tissue, NPY^+ neurons in the NTS, POMC-expressing neurons in the ARH and orexin or MCH-expressing neurons in the LH send projections to the liver[129]. Thus, there are specific neuronal populations in the NTS and hypothalamus that signal to both the adipose tissue and liver, either separately or simultaneously.

Some studies have assessed whether neuroendocrine signaling in the CNS can affect hepatic inflammatory state. For example, orexin-deficient mice fed a high fat diet have heightened markers of inflammation, including NFκB, JNK and p38 phosphorylation and CCL2 and CD11c expression, in the liver, compared with wild-type controls; however

intracerebroventricular administration of orexin A was able to alleviate these effects[141]. Moreover, central orexin A infusion inhibits high fat-induced hepatic inflammation and hyperphagia-induced systemic insulin resistance[141,142]. Chemogenetic activation of orexin-expressing neurons in the LH upregulates mTOR and downstream S6 kinase activity, and elevates spliced X-box binding protein 1 (sXBP1) expression in the liver, which is suggested to protect against hepatic inflammation and endoplasmic reticulum stress[141]. Notably, CSDS in mice reduces orexin expression, the number of orexin-positive neurons and the activation of these neurons in the LH[143], while intracerebroventricular orexin infusion or chemogenetic activation of LH orexin$^+$ neurons rescues stress-induced anxiety behaviour in the open field test, immobility in the forced swim test and social avoidance[144,145]. This implies that chronic psychosocial stress dampens orexin signaling in the brain, leading to hepatic inflammation, macrophage infiltration, hyperglycemia and depression- and anxiety-like behaviour. From the LH, these effects may be exerted through parasympathetic neurons in the DMV, as LH orexin neurons project to the DMV[146] and parasympathetic input from the vagus nerve dampens hepatic inflammation[147]. Indeed, chemogenetic activation of DMV neurons lowers hepatic lipid accumulation and macrophage numbers in a mouse model of non-alcoholic steatohepatitis (NASH)[148]. Collectively, these studies illustrate a pathway through which a psychological state such as stress could impact signals from LH orexin neurons to parasympathetic nerves via the DMV to cause hepatic inflammation, which contributes to insulin resistance (Fig. 2).

Brain signals and immunosuppression

It is commonly reported that chronic stress compromises immune function, increasing susceptibility to infection[149]. Similar to humans with MDD, stressed mice are also more susceptible to infections by pathogens such as *Escherichia coli*, influenza and SARS-CoV-2[69,150,151]. While acute stressors or infections activate the HPA axis, which stimulates the immune system to facilitate clearance of pathogens, chronic stress has immunosuppressive effects[152]. This exemplifies how stress is a context-dependent adaptation that is necessary for the body to appropriately respond to threats, but becomes maladaptive and pathological when left unresolved. Likewise, in behavioural tasks, there is a proposed ‘inverted U-shape’ curve describing the relationship between stress levels and performance, suggesting that there is an optimal level of stress (which may also shift based on prior stress exposure)[153]. Mechanistically in the immune system, leukocytes express glucocorticoid receptors that can respond to cortisol and other glucocorticoids[154]. It is hypothesized that chronic stress leads to persistent activation of the HPA axis, resulting in glucocorticoid resistance and subsequent over-production of pro-inflammatory cytokines and impairment in adaptive immune responses[154]. Together, these maladaptations worsen outcomes of infectious disease.

Chemogenetic tools have been used to demonstrate that activation of specific neurons in the brain, independent of stress exposure, is sufficient to heighten vulnerability to infections. For example, excitation of CRH$^+$ neurons in the PVH prevented pulmonary clearance of influenza A virus, implicating the HPA axis in this response[69]. Similarly, high pulmonary viral loads were observed in restraint-stressed mice; however, ablating PVH CRH$^+$ neurons ameliorated the immunosuppression brought upon by stress[69]. Exposure to

restraint stress, activation of PVH CRH^+ neurons and susceptibility to influenza A were also associated with diminished B and T cell numbers in lung-draining lymph nodes, which supports the idea that HPA axis activity represses adaptive immunity[69]. In agreement with these findings, a separate study found that optogenetic stimulation of CRH^+ neurons in the PVH shifts circulating leukocytes to an 'immunosuppressed' profile, characterized by lower frequencies of dendritic cells expressing major histocompatibility complex (MHC) class II molecules, natural killer cells, B cells, and $CD4^+$ T cells[155]. In parallel, anther study demonstrated that activating the brain's reward systems by chemogenetically exciting TH^+ VTA neurons enhances peripheral bactericidal action against *E. coli*, while promoting social interaction[72]. Infections can produce 'sickness behaviour', which is characterized by behaviours such as anhedonia, lethargy and social withdrawal[4]. Interestingly, sepsis results in acute activation of BNST-projecting neurons in the CeA, along with long-term anxiety-like behaviours in the open field test and light-dark box[156]. When a chemogenetic approach is used to inactivate BNST-projecting CeA neurons, these mice become protected against sepsis-induced sickness behaviours[156]. These studies demonstrate bi-directional communication between the brain and body, whereby chronic stress suppresses host defense against pathogens and these infections subsequently activate brain regions that promote anxiety- or depression-like behaviour (Fig. 2).

Conclusions

For years, the mechanisms through which a psychological state can influence peripheral immunity have been puzzling. Due to recent developments in neurocircuit tracing, chemogenetic and optogenetic tools for manipulating specific neuronal circuits and immunophenotyping of peripheral tissues, the field is beginning to understand the complex ways in which the brain and body communicate in healthy and diseased states. Under chronic stress, regions such as the hypothalamus, amygdala and insula are pivotal structures that integrate signals in the CNS and then propagate them to the periphery, largely via the autonomic nervous system and HPA axis. Additional studies are required to decipher how context-specific cues deliver information from the brain to different peripheral tissues to shape immunological function, and to further dissect which brain regions can influence systemic inflammation upon activation.

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Glossary

Cytokines

Secreted proteins that act as signaling molecules for the immune system

Lymphopoiesis
The production of lymphocytes from progenitor cells

Myelopoiesis
The production of myeloid cells from progenitor cells

Chemokines
Chemotactic cytokines that stimulate migration of cells

Viral tracing
The use of trans-synaptic self-replicating viruses to identify neural pathways

Granulocyte
Leukocytes containing cytoplasmic secretory granules, such as neutrophils, basophils, and eosinophils

Plasma cells
Effector B lymphocytes that produce antibodies

Leukocytes
A type of blood cell made in the bone marrow and found within blood and lymphoid tissue as part of the immune system

Monocytosis
An increase in the number of monocytes in the blood

Neutrophilia
An increase in the number of neutrophils in the blood

Lymphocytopenia
A reduction in the number of lymphocytes in the blood

Splenomegaly
An enlargement of the spleen

Chemogenetics
An approach in which specific cellular pathways are activated or inhibited using engineered protein receptors that respond to previously unrecognized small molecules

Optogenetics
An approach in which light-sensitive ion channels, pumps or enzymes areused to regulate the activity of specific neurons in the brain or periphery

Ventral tegmental area (VTA)
A ventral midbrain site containing dopaminergic neurons that are an essential component of the brain’s reward circuitry

Reward

A positive emotional stimulus. In psychological terms, a reward is reinforcing — it promotes repeated responding to obtain the same stimulus

Resilience

The ability to maintain normal physiological and behavioural function in the face of severe stress

Susceptible

Having increased vulnerability to succumb to the deleterious effects of stress

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Box 1.

Animal models of chronic stress

The field typically uses three standardized chronic stress paradigms in adult C57BL/6J mice — chronic social defeat stress (CSDS), adult social isolation (ASI) and chronic variable stress (CVS). In all three paradigms, certain behavioural abnormalities are induced that can be reversed by chronic (but not acute) antidepressant treatment[189–191]. Importantly, all three paradigms have been validated in both male and female mice, making it possible to study sex differences[192–194]. In some paradigms, the two sexes display similar behavioural responses, but in others, large differences are seen. RNA sequencing (RNA-seq) has shown that each model induces many distinct gene expression changes within limbic brain regions, with each model replicating a partly distinct subset of the changes that have been observed in homologous brain regions of humans with depression[195].

Chronic social defeat stress (CSDS).

10 days of social stress induced by daily exposure to a dominant, aggressive mouse promotes a behavioural syndrome characterized by social avoidance, reduced responses to natural rewards, altered exploratory behaviour, systemic inflammation, disrupted circadian rhythms, a hyperactive hypothalamic–pituitary–adrenal (HPA) axis and metabolic syndrome[25,196–198]. CSDS offers several major advantages compared with other available chronic stress paradigms. First, about one third of C57BL/6J mice subjected to CSDS escape most of these symptoms and show deficits in exploratory behaviour only[197]. These mice are referred to as ‘resilient’ and can be compared to the majority, which are ‘susceptible’ (SUS). Second, many of the behavioural symptoms exhibited by SUS mice are very long-lived (some persist for at least six months after CSDS), which makes it possible to study the reversal of stress-induced pathologies by traditional antidepressants as opposed to prevention of such pathologies — the norm for the other paradigms. Third, only about half of SUS mice show reversal of behavioural abnormalities in response to either chronic administration of standard antidepressants (such as imipramine (IMI), fluoxetine (FLX) or bupropion) or acute administration of novel antidepressants (such ketamine), with the other half being ‘treatment-resistant’. CSDS thus enables studies of treatment response versus non-response. We and our collaborators have also developed several critical derivations of CSDS, including a ‘vicarious defeat’ model, in which a mouse witnesses the physical defeat of a conspecific C57BL/6J mouse and develops a syndrome very similar to that of the physically defeated mice (thus removing the confound of the physical fighting when analyzing stress effects)[199] and standard and witness models of social defeat for female C57BL/6J mice[192,200,201]

Adult social isolation (ASI).

Adult male or female C57BL/6J mice housed for prolonged periods (>8 weeks) in isolation exhibit reduced preference for natural rewards (sucrose consumption and sexual behaviour) and social interaction[191,194,202,203], with very similar abnormalities seen in males and females. The latter symptoms only are prevented by concomitant, chronic

exposure to antidepressants. Interestingly, RNA-seq analysis of bulk brain tissue after ASI or CSDS has shown that some genes are affected in both paradigms, but that the transcriptomic responses are mostly different[203]; as noted above, we believe that the two paradigms model distinct aspects of human stress-related syndromes that are characterized by active versus passive stress, although this remains speculative.

Chronic variable stress (CVS).

A variety of CVS (also referred to as chronic mild or unpredictable stress) paradigms are used by the field[190,204–207]. One particular paradigm can cause reduced sucrose preference and increased novelty suppressed feeding among other pro-stress phenotypes in both male and female C57BL/6J mice, although the model also works in other mouse strains[208]. In this protocol, females are more susceptible: they show behavioural symptoms after 6 days of CVS, at which time males appear normal, while both sexes show similar behavioural symptoms after 21 days of CVS. This is a major advantage of the CVS protocol, given that depression is twice as common in women.

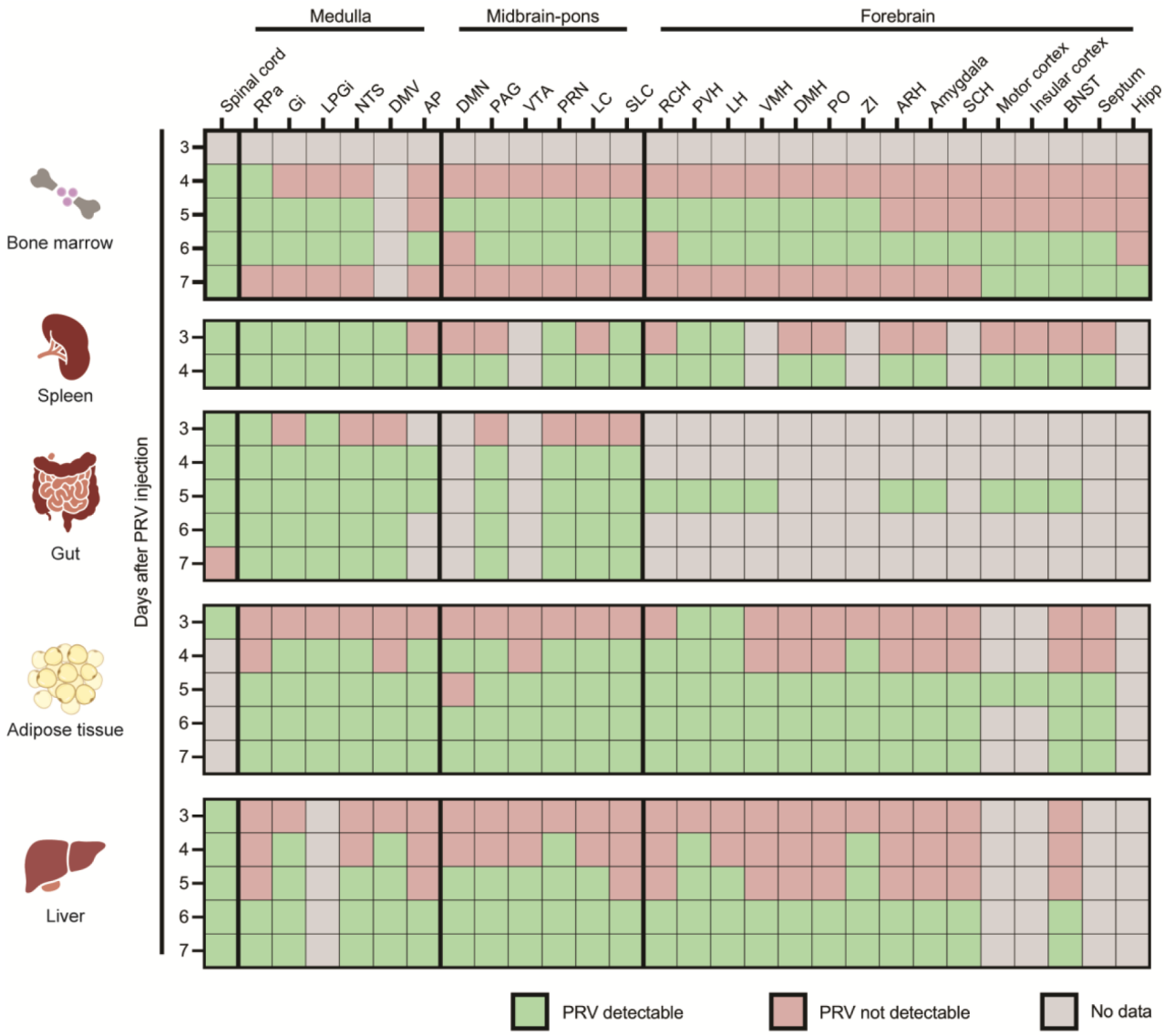

Fig. 1: CNS innervation of immunologically-relevant peripheral tissues.

Summary of time course studies identifying CNS regions innervating the bone marrow[37,38], spleen[80,81], gut[90–92], adipose tissue[128,129] and liver[129,139] following trans-synaptic retrograde tracing using pseudorabies viruses (PRVs). CNS regions where PRV was identified are shown on the x-axis, with days after PRV injection indicated on the y-axis. AP, area postrema; ARH, arcuate nucleus of the hypothalamus; BNST, bed nucleus of the stria terminalis; DMH, dorsomedial nucleus of the hypothalamus; DMN, deep mesencephalic nucleus; DMV, dorsal motor nucleus of the vagus; Gi, gigantocellular reticular nucleus; Hipp: hippocampus; LC, locus coeruleus; LH, lateral nucleus of the hypothalamus; LPGi, lateral paragigantocellular nucleus; NTS, nucleus of the solitary tract; PAG, periaqueductal grey; PO, preoptic area; PRN, pontine reticular nucleus; PVH, paraventricular nucleus of the hypothalamus; RCH, retrochiasmatic nucleus; RPa, raphe pallidus; SCH, suprachiasmatic nucleus; SLC, subcoeruleus nucleus; VMH, ventromedial nucleus of the hypothalamus; VTA, ventral tegmental area; ZI, zona incerta.

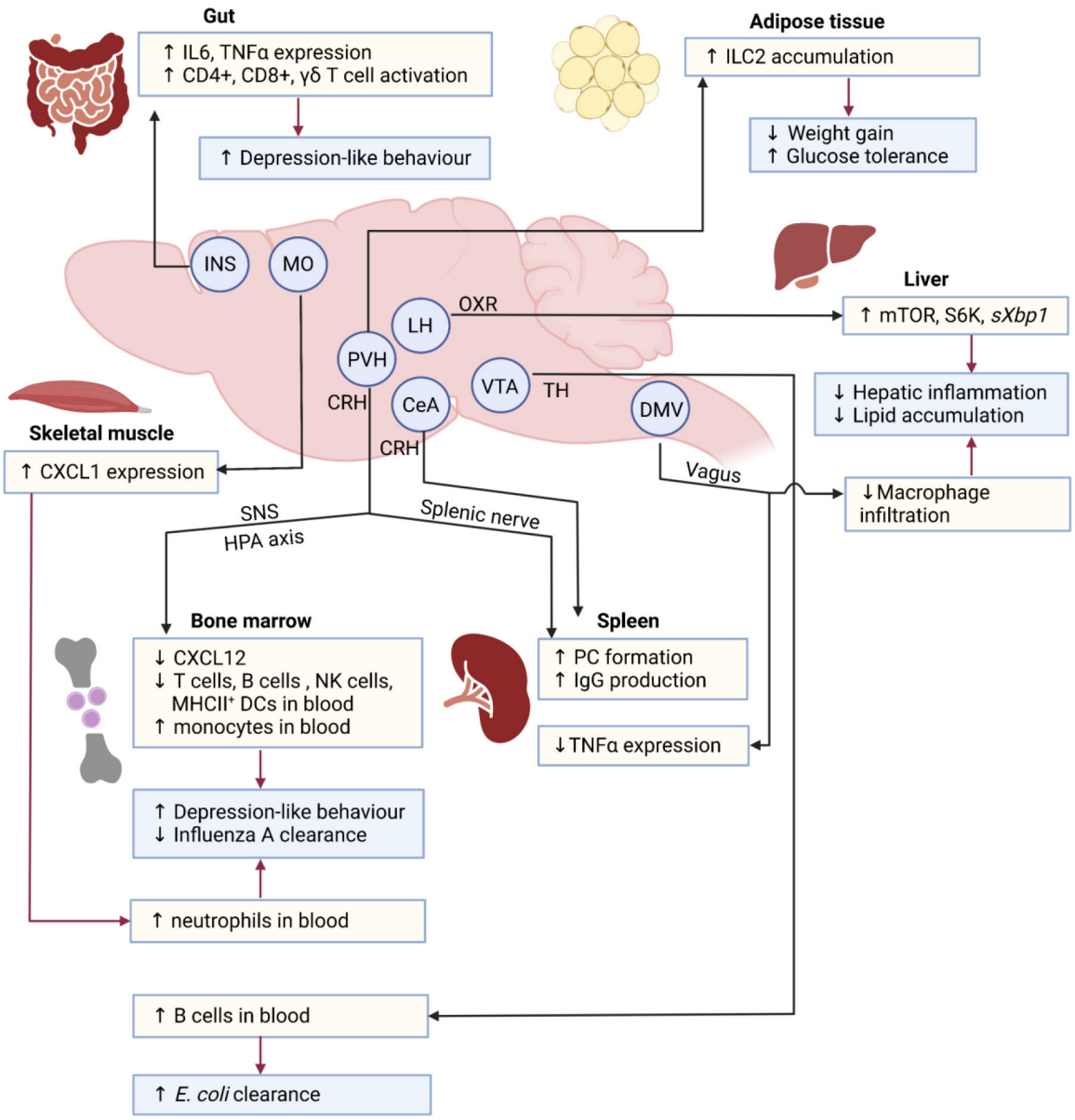

Fig. 2: Control of peripheral immunity by central stress centres.

Schematic outlining the regulation of peripheral immune responses by CNS regions involved in stress and reward processing. Activation of the paraventricular nucleus of the hypothalamus (PVH) decreases bone marrow chemokine (C-X-C motif) ligand 12 (CXCL12) expression, induces monocytosis and lymphocytopenia, increases splenic plasma cell (PC) formation and IgG production, and promotes the accumulation of type 2 innate lymphoid cells (ILC2) in adipose tissue through activation of the HPA axis, SNS, or splenic nerve[33,69,80,133]. Motor circuit activity, driven by the motor cortex (MO) stimulates neutrophilia via skeletal muscle production of cytokines such as CXCL1[69]. Monocytosis, neutrophilia and leukocytopenia contribute to depression-like behaviour and impair influenza A clearance. Adipose tissue ILC2s are associated with decreased weight gain and improved glucose tolerance. Ventral tegmental area (VTA) stimulation increases

the numbers of B cells in circulation to improve bacterial clearance[72]. Central amygdala (CeA) CRH neuron stimulation also contributes to PC formation[80]. Dorsal motor nucleus of the vagus (DMV) activation, acting via the vagus nerve, inhibits tumour necrosis factor α (TNF) expression in the spleen and macrophage infiltration in the liver[83,148]. Orexin (ORX) expression in the lateral nucleus of the hypothalamus (LH) also upregulates mTOR, S6K and *sXbp1* in the liver to limit hepatic inflammation[141]. Insular cortex (INS) neurons drive processes that can trigger inflammatory responses in the colon, including activation of CD4+, CD8+, and γδT cells, and expression of IL6 and TNF[101]. HPA axis: hypothalamic-pituitary-adrenal axis, SNS: sympathetic nervous system, CRH: corticotropin-releasing hormone, mTOR: mammalian target of rapamycin, S6K: S6 kinase, *sXbp1*: spliced X-box binding protein 1.

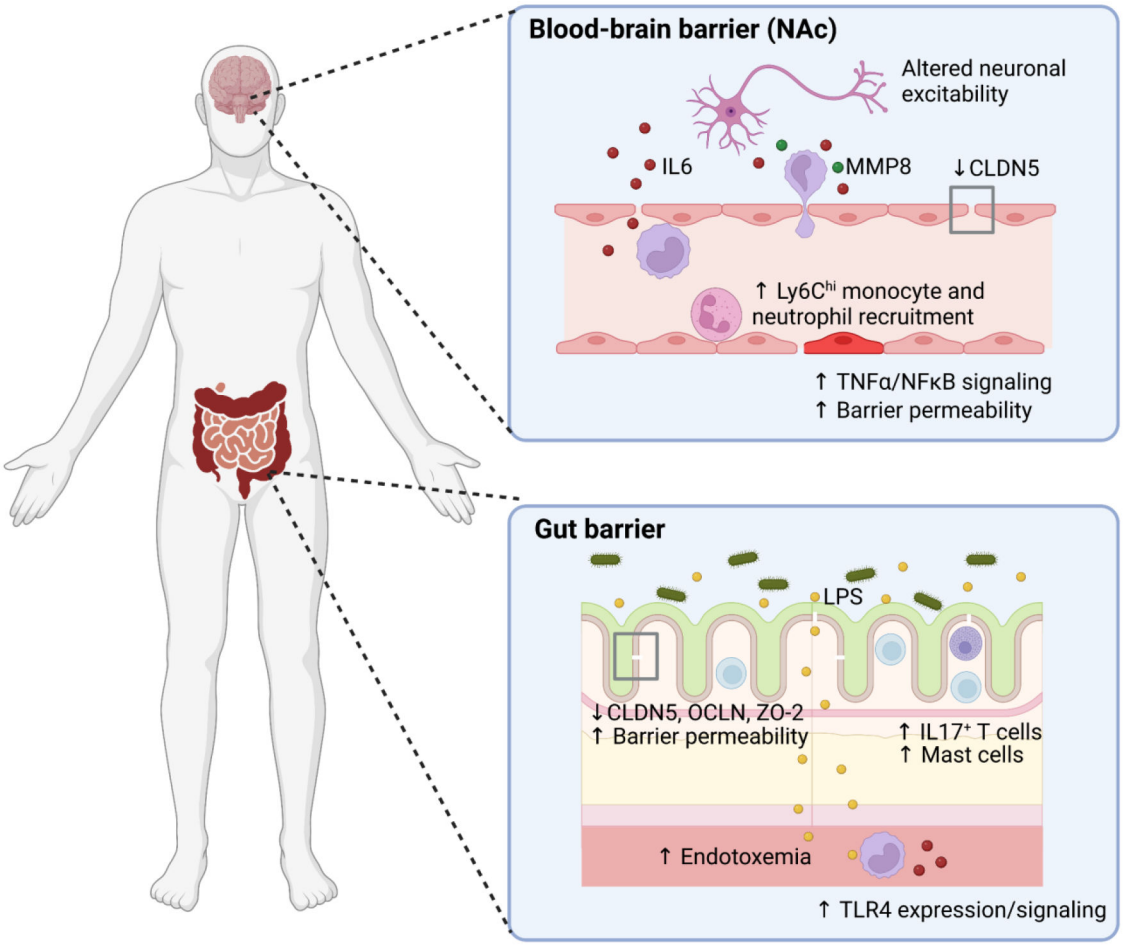

Fig. 3: Breakdown of body barriers during stress [.

Chronic stress or stress-relevant disorders, such as anxiety and depression, compromise the blood-brain barrier (BBB) and gut epithelial barrier. In the nucleus accumbens (NAc), stress triggers pro-inflammatory tumour necrosis factor α (TNF) and/or nuclear factor-κB (NFKB) signaling pathways in endothelial cells and downregulation of the tight junction protein claudin-5 (CLDN5)[7,74]. Simultaneously, inflammatory monocytes expressing high levels of Ly6C (Ly6C^{hi} monocytes) and neutrophils are recruited to the NAc, where these cells (or their secreted factors, such as interleukin 6 (IL6) and matrix metalloproteinase 8 (MMP8)) can enter the brain parenchyma through the damaged BBB to directly influence neuronal excitability[7,76]. In the intestine, stress increases IL17^{+} T cell and mast cell accumulation, which may contribute to decreases in CLDN5, occludin (OCLN), and tight junction protein 2 (ZO-2), allowing lipopolysaccharide (LPS) to enter circulation from the gut lumen to activate pro-inflammatory signaling pathways via toll-like receptor 4 (TLR4)[95,106–108].

Table 1.

Serum cytokines and chemokines elevated in depression, anxiety and co-morbid disorders

Human disorder	Cytokines and chemokines elevated in humans	Mouse model	Cytokines and chemokines elevated in mice	References
Depression and /or anxiety	IL1A, IL1B, IL2, IL6, IL8, IL12, IFNγ, TNF, CCL2, CCL3, CCL11, CXCL4 and CXCL7	Chronic stress	IL1A, IL1B, IL6, IL12, TNF, CCL2, CCL5, CXCL1 and CXCL2	21–25,27–31,157
Inflammatory bowel disease	IL1B, IL4, IL5, IL6, IL7, IL8, IL10, IL12, IL13, IL15, IL16, IL17, IL23, IFNγ, TNF, MIF, CCL2, CCL11, CCL21, CCL23, CCL25, CXCL1, CXCL5, CXCL6, CXCL10, CXCL11 and CXCL13	Experimental colitis	IL1B, IL6, IL12, IL17, IFNγ, TNF, CCL2, CCL3 and CXCL1	158–164
Metabolic syndrome and/or obesity	IL1B, IL4, IL5, IL6, IL8, IL10, IL12, IL13, IL18, IFNγ, TNF, CCL2, CCL3, CCL5 and CXCL5	Diet- or genetically-induced obesity	IL1B, IL6, IL12, IL18, IFNγ, TNF, CCL2, CXCL1 and CXCL5	165–178
Coronary artery disease and/or atherosclerosis	IL1A, IL1B, IL2, IL6, IL8, IL9, IL10, IL17, IFNγ, TNF, CCL2, CCL5, CCL17 and CCL18	*ApoE*$^{-/-}$ or *Ldlr*$^{-/-}$ mice	IL1A, IL1B, IL2, IL6, IL10, IL12, IFNγ, TNF, CCL2, CCL5 and CXCL1	178–188

CCL: chemokine (C-C motif) ligand, CXCL: chemokine (C-X-C motif) ligand, IFN: interferon, IL: interleukin, MIF: macrophage migration inhibitor factor, TNF: tumour necrosis factor