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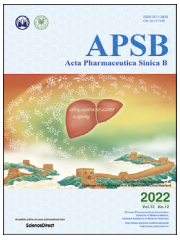

COMMENTARY

Commentary: Acute psychological stress redistributed leukocytes *via* distinct brain circuits

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It is commonly known that psychological stress affects immunity through the nervous system, but the specific stress networks between brain and peripheral leukocytes, or their relationship with disease initiation or progression have yet to been delineated. A recent study by Poller and his colleagues[1] propose an innovative perspective that distinct brain circuits rapidly manipulate a large-scale whole-body re-distribution of leukocytes (neutrophils, monocytes, lymphocytes) during psychological stress. Using acute restraint stress, a well-accepted model mimics psychological stress in mice, the authors found an early period of opposing leukocyte flux in the peripheral blood, which is consistent with the previous research[2]. Peak neutrophilia was found to be induced 1 h after a restraint stress lasting just 30 s. In contrast, a reduction in blood monocytes and lymphocytes was observed, which required at least 4 h of restraint stress. Such acute stress-induced the changes to blood leukocyte levels were accounted for the migration of monocytes and lymphocytes from peripheral tissues to the bone marrow by a process referred to as leukocytes homing, which was contrasted by mobilization of neutrophils from the bone marrow to the peripheral circulation. Using an intricate series of experimental designs, the authors determined that stress-induced shifts in blood monocytes and lymphocytes were affected by hypothalamic–pituitary–adrenal (HPA) axis and stress hormone corticosterone, *via* augmentation of C–X–C chemokine receptor 4 (see Fig. 1)

The paraventricular nucleus of hypothalamus (PVH), is an important region of the HPA axis that is active during acute stress. The authors showed that specific activation of corticotropin releasing hormone (CRH) neurons in PVH increased

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corticosterone levels to reduce monocytes and lymphocytes in peripheral circulation. This effect was disappeared in PVH-CRH ablated neurons, and in CRH knockout animals. Taking together, the authors concluded that the PVH/CRH axis is essential for stress-induced homing of monocytes and lymphocytes to the bone marrow. On the other hand, the authors determined that acute stress-induced neutrophilia could not be explained by the above mechanism since neutrophil mobilization was independent of HPA and sympathetic nervous system.

Searching for a potential mechanism that drives brain control of stress-induced neutrophilia, the authors identified an association between the increased serum levels of C−X−C motif chemokine ligand 1 (CXCL1) and the dynamics of neutrophil migration to the peripheral circulation. Intriguingly, they identified the skeletal muscle as the source of this CXCL1. Augmentation of skeletal muscle CXCL1 was found to be a unique response to stress because no increases in CXCL1 were observed in response to voluntary running, nor was there any indication of muscle damage after restraint stress.

These observations implied that while on the one hand, acute stress-mobilized peripheral blood neutrophils might participate in the onset inflammation, on the other hand, lymphocytes were prevented from occupying lymph nodes, potentially to limit the adaptive immune response. The counter-directional shift of leukocytes provoked by stress is thus reminiscent of the Yin−Yang balance disturbance, a central tenet in traditional Chinese medicine theory. Here, neutrophils represent the Yin with negative effect, and lymphocytes represent the Yang with positive effect in peripheral circulation.

There has been increasing attention on the relevance of psychological stress on susceptibility to viral infections[3,4] and cancer[5] diseases, which are closely associated with disruption of immunity. To obtain insight on the potential implications of acute stress-induced leukocyte mobilization and redistribution on immune system associated diseases, the authors employed mouse models of autoimmunity (experimental autoimmune encephalomyelitis) and viral infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza A virus (IAV) infections. Remarkably, they determined that acute stress protected against initiation and progression of autoimmunity by activating specific brain regions involving the CRH neurons in the PVH. On the other hand, acute stress impaired host adaptive immunity against SARS-CoV-2 and IAV infection. Thus, acute stress can exert either positive or negative effects on diseases through leukocyte mobilization. As nicely demonstrated in this manuscript, these effects are enforced by different brain regions and neural circuits that drive the acute stress response. Better understanding the mechanistic of psychological stress on immune

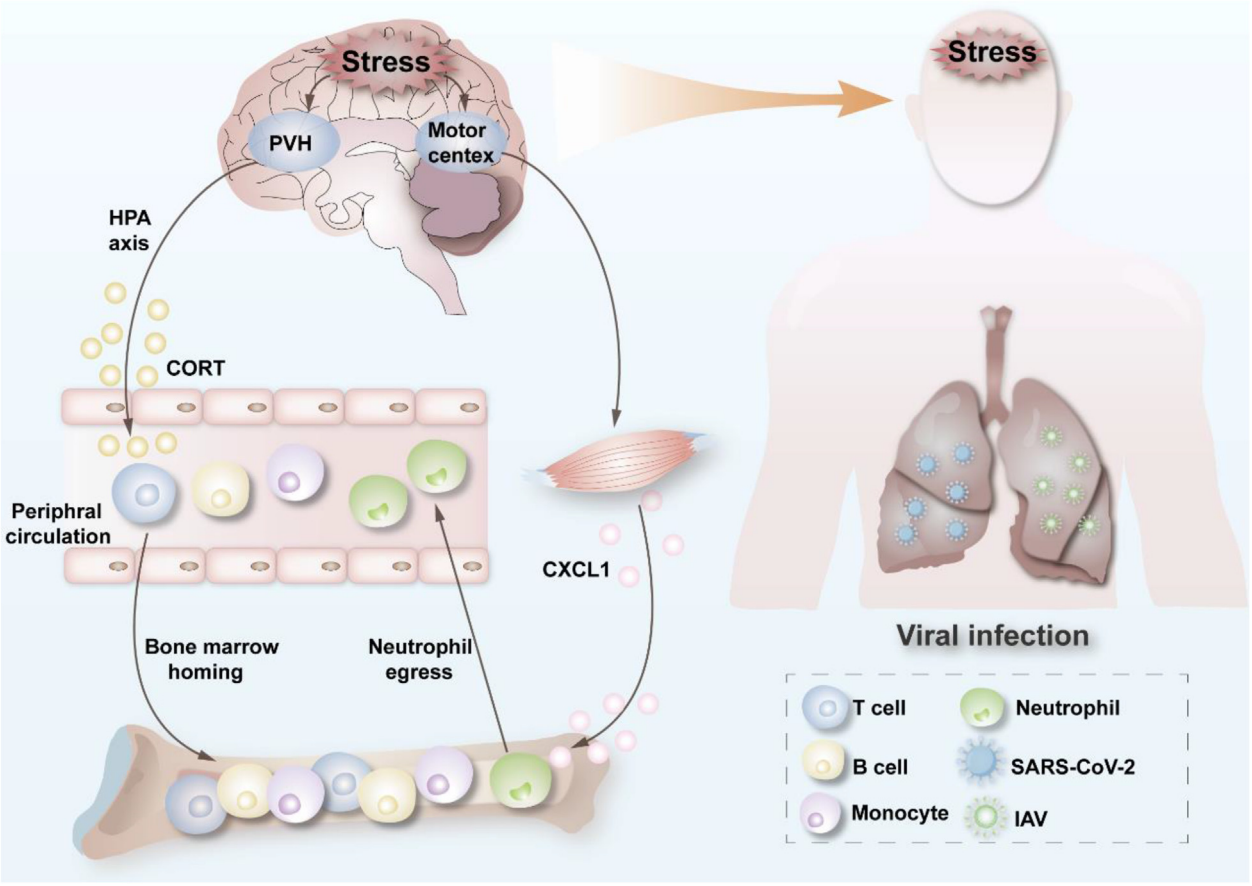

Figure 1 Schematic illustration of psychological stress redistributed leukocytes *via* distinct brain circuits in viral infection. Acute stress-transiently prevented monocytes and lymphocytes from occupying peripheral circulation through the HPA axis, while, mobilizing neutrophils into peripheral circulation *via* motor cortex-mediated skeletal muscle releasing CXCL1, which together leads to viral (SARS-CoV-2 and IAV) infections. Abbreviations: PVH, paraventricular hypothalamus; CORT, corticosterone; CXCL1, C−X−C motif chemokine ligand 1; HPA axis, hypothalamic−pituitary−adrenal axis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IAV, influenza A virus.

system will provide helpful insight into the effective control and treatment of different diseases. There are a variety of means by which selective control stress induced redistributed leukocytes, might be realize by selective inhibiting the activation of CRH neurons in the PVH, blocking the lymphocyte and monocyte migration by CXC chemokine receptor 4, or restraining neutrophil mobilization by repressing CXCL1 secretion from muscle. These may be critical for translating knowledge of the communication between neural network and stress response into therapies and could be impactful on alleviating stress-induced disease susceptibility.

Acknowledgments

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