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The shape of things to come: early life stress stunts brainstem microglia with lasting implications for cardiorespiratory control and plasticity

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Early life stress affects cardiorespiratory control, with maladaptive consequences that can be long-lasting. Interestingly, sex-specific outcomes are evident on occasion, revealing male susceptibility to perinatal perturbation, responses resulting from stress-related neuroendocrine dysregulation. One such example is the clinically-relevant stressor of neonatal maternal separation (NMS), which disrupts respiratory network control with resultant aberrant responses to arterial and airway chemoreflex activation. In adult male rats, antecedent exposure to NMS increases respiratory instability and augments hypoxic ventilatory responsiveness, effects which persist across the sleep-wake cycle (Kinkead et al., 2009). Prolonged apnoeas evoked by the laryngeal chemoreflex in NMS-exposed rat pups are associated with augmented reflex bradycardia and oxygen desaturation compared with controls, especially in males (Baldy et al., 2018a). Indeed a portfolio of problems persists following perinatal stress, suggesting considerable network remodelling beyond altered neuromodulation, probably at multiple loci, culminating in a curtailed capacity to establish and preserve cardiorespiratory homeostasis.

In this issue of *Experimental Physiology*, Baldy et al. (2018b) reason that enhanced frequency and amplitude of excitatory post-synaptic potentials in the dorsal motor nucleus of the vagus (DMNV) of NMS-exposed male rat pups (Baldy et al. 2018a) potentially arises from stress-related inadequate pruning of synapses by microglia, resident immune cells of the CNS, critical in the dynamic formation of developing networks to efficient functional circuits. Developing microglia are phenotypically distinct, proliferating during the second week of postnatal life in rodents. Brain microglia are substantively shaped by the micro- and macro-environment and are responsive to stress and sex hormones in a region-specific manner (Lenz & Nelson, 2018). Early life stress perturbs microglial maturation, which is suggested to have relevance to developmental trajectories and a variety of altered behaviours (Lenz & Nelson, 2018). It is now recognised that neuroimmune interactions modulate respiratory control, but hitherto, whether NMS affects brainstem medullary microglial density and maturity was not known. In view of a growing appreciation of the pivotal role of the immune system in early life programming of brain and behaviour, Baldy et al. (2018b) set out to establish if NMS affects microglial density and arborisation in the caudal nucleus tractus solitari (cNTS)

and DMNV, two key medullary regions relevant to stress-dependent plasticity in cardiorespiratory control.

Using an established model of NMS (Baldy et al., 2018a), pups were separated from their dam for 3 hours per day from postnatal days 3 to 12. Microglia number and morphometry were systematically determined in standardized regions of interest in sections of cNTS and DMNV by immunolabelling using the specific marker, Iba-1. In medullary homogenates, the abundance of the neural-derived fractalkine (CX_3CL_1) and its unique receptor (CX_3CR_1) expressed by microglia, was determined by immunoblotting. Fractalkine signalling through CX_3CR_1 is an important modulator of microglial migration and their scope for synaptic sculpting. Baldy et al. (2018b) report a significant increase in the density of microglia in NMS pups compared with controls, both in the cNTS and DMNV medullary regions. The microglia of NMS pups displayed significant reduction in arborisation area and a proportionate increase in cell soma area, particularly in the DMNV. Surprisingly, there were no sex differences. CX_3CR_1 abundance was unaffected by NMS, but was significantly greater in male pups compared with female pups. Neither sex nor stress affected CX_3CL_1 abundance. The authors posit that the condensed amoeboid shape of the microglia from NMS pups reflects an immature phenotype in the developing brain, revealing stress-related stunting of medullary microglia. The molecular mechanism orchestrating this response remains unclear but appears unrelated to fractalkine signalling, a surprise in the light of observations of stress-related sex-specific reductions in mouse hippocampal CX_3CR_1 mRNA expression, with evidence of impaired synaptic pruning and behavioural changes (Fernández de Cossío et al., 2017).

The findings of Baldy et al. (2018b) should ignite interest and inquiry in the nascent field of developmental neuroimmunology, which now extends to brainstem networks critical in the control of cardiorespiratory function. It is understood that assessment of microglial morphometry alone is limited, serving as a proxy of innate immune cell activity. Comprehensive screening of medullary microglia in a variety of models of early life adversity is now warranted. Also, before excluding fractalkine signalling in NMS-related medullary microglial dormancy, it is necessary to explore region-specific CX_3CR_1-dependent signalling within the brainstem, and in particular within the DMNV. Other observations by Baldy et al. (2018b) suggesting “unique” properties of medullary microglia provide a rich tapestry for future investigation. The anticipated advent of experimental tools to (focally) manipulate microglial function will expedite and widen understanding in the field. It is also worth emphasizing that integrative cardiorespiratory parameters provide robust and reliable measures to assess fundamental aspects of stress-related neuroimmune interaction in the developing nervous system.

At this early juncture in a rapidly evolving storyline, it appears that neonatal stress affects medullary microglia in a manner consistent with adverse physiological outcomes, albeit that the surprising lack of a sex difference is incongruent with functional changes previously documented by this group (Baldy et al., 2018a). Stress-related stunting of microglia may have direct implications for respiratory network stability and responsiveness, which are especially malleable in the vulnerable period of postnatal development. Moreover, what should also be appreciated is the potential for perpetual cardiorespiratory stress arising from early life adversity, which may compound deleterious outcomes for brain and body.

Competing Interests

None.

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