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VIEWPOINT

Damage control: carotid body activation and remodelling in response to aseptic tissue injury

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carotid body, damage-associated molecular patterns, inflammation, gene expression, hypoxia

The carotid body (CB) is a key sensory organ lying near the carotid bifurcation that constantly monitors composition of blood supplying the brain, looking for potentially dangerous or harmful stimuli. The most well characterised stress stimulus is hypoxia. Upon stimulation by hypoxia, the CB responds within seconds by sending thousands of nerve impulses into the brainstem causing rapid activation of vital cardiovascular and respiratory reflexes including vasoconstriction, elevated heart rate and increased breathing (Holmes et al., 2019). These reflexes enable maintenance of enough blood oxygen to be delivered to the brain and vital organs to support survival during this critical situation. This has never been more important than in the current COVID-19 pandemic in which millions of patients have been exposed to acute and chronic hypoxia and were reliant on the reflexes initiated by the CB to support their own survival. Whether dysfunctional or desensitised CBs are implicated in increased vulnerability and poor clinical outcomes in COVID-19 is an important consideration that requires urgent attention. In addition to hypoxia, it is becoming more apparent that the CB also responds to other threatening stimuli including hypercapnia, acidosis, hypoglycaemia and the stress hormone adrenaline (Thompson et al., 2016). In this issue of *Experimental Physiology*, Mkrtchian and co-workers now provide the first evidence that the CB is able to detect and respond to damage-associated molecular patterns (DAMPs) – key inflammatory mediators released into the systemic circulation upon aseptic cell/tissue injury or death (Mkrtchian et al., 2020). This is an exciting and timely translational study that uses a range of *in vivo*, biochemical and genetic approaches to emphasise the importance of immune signalling in regulating CB function and remodelling in this novel context.

In their initial experiments, the authors demonstrate that exogenous application of two well-known DAMPs, high mobility group box 1 (HMGB1) and S100 A8/A9, to *ex vivo* isolated rat CBs causes an elevation in extracellular dopamine, consistent with CB stimulation and neurotransmitter release (Mkrtchian et al., 2020). To strengthen these findings and increase the translational impact, the investigators then obtained plasma from animals following tibial surgery, a well-established model of aseptic tissue injury. When this conditioned plasma was applied to CBs in culture, again there was an increase in dopamine release, at a level similar to that observed with the exogenous DAMPs. Thus, this work reveals that DAMPs and tissue injury act as novel CB chemostimulants. In addition, DAMPs and the conditioned plasma both significantly elevated tumour necrosis factor (TNF) α, indicative of similar immunostimulation. What is surprising is that although dopamine was consistently elevated in both experimental settings, other key excitatory neurotransmitters (ATP and acetylcholine) showed considerable variation and in some instances were not elevated at all. Given that dopamine is an inhibitory neurotransmitter in the CB, whilst ATP and acetylcholine are excitatory, the full functional impact of DAMPs and tissue injury

in terms of modifying chemoafferent activity remains somewhat uncertain. It is important to emphasise that it is the chemoafferent outflow from the CB that will ultimately determine whether or not DAMPs are able to initiate reflex stimulation leading to modifications in cardiovascular and respiratory function. That said, it could also be that dopamine is more abundantly expressed, has greater stability and is released in greater quantities than both ATP and acetylcholine and so offers a more reliable assay. Dopamine secretion is still regarded as the gold standard and most reliable assay for measuring transmitter release in the CB. It is well known that dopamine is released in large quantities in response to other excitatory stimuli including hypoxia. Thus, there is a clear need now to extend these findings and perform subsequent studies evaluating the impact of DAMPs and tissue injury on CB chemoafferent activity and cardiovascular/respiratory function including measurements of ventilation, heart rate and vascular blood flow. These exciting findings also need validation in humans, which will be an important next step.

Using elegant and highly skilled cutting-edge molecular biology techniques, the authors go on to evaluate the impact of DAMPs on gene expression in the CB. Both exogenous application of HMGB1 and the conditioned plasma evoked significant alterations in gene expression, measured using RNA sequencing (Mkrtchian et al., 2020). Thus, exposure to DAMPs and tissue injury not only evokes acute CB activation, but also has the potential to produce long term CB remodelling. To help with functional interpretation, the investigators performed a gene ontology analysis which groups differentially regulated genes and estimates the specific cellular functions that are most likely to be altered. Key processes suggested to be modified following application of HMGB1 are immune and inflammatory responses as well as cytokine–cytokine receptor interaction. This was in contrast to that observed following exposure to conditioned plasma which rather suggested that the most highly affected pathways were specifically related to TNF and nuclear factor κB signalling. Whilst there is some overlap, these data are indicative of differing responses at the gene expression level between HMGB1 and the conditioned plasma. This is supported by the finding that many more genes are differentially expressed in response to conditioned plasma treatment compared to HMGB1 alone. It also implies that that gene expression changes in the CB caused by peripheral tissue injury are not only due to HMGB1. The identity of these other, as yet unknown, mediators is intriguing and warrants further evaluation. Although this study focused on HMGB1 and S100 A8/A9 there are many more DAMPs known to exist that are still to be assessed in the CB.

Previous studies have shown that the CB is also able to sense and respond to both local and systemic inflammation under different circumstances with the potential to subsequently alter cardio-respiratory homeostasis (Iturriaga, Moya, & Del Rio, 2015). This could have important implications for impaired/resetting of cardiovascular and respiratory control in numerous important chronic low-grade inflammatory diseases such as obesity, metabolic syndrome, diabetes, chronic obstructive pulmonary disease and obstructive sleep apnoea, to name just a few. The CB can also be activated by acute inflammatory events initiated upon invasion by foreign pathogens. It has been shown that the CB type I cells (the sensory cells in the CB) are able to directly sense pathogen-associated molecular patterns (PAMPs), via expression of toll-like (TLR-2 and TLR-4) and interleukin 1 receptors, similar to those expressed on neutrophils, evoking an immediate and substantial elevation in ventilation (Ackland, Kazymov, Marina, Singer, & Gourine, 2013). Thus, the importance of immune signalling in the CB is starting to emerge and many more studies are expected in this area. The study by Mkrtchian and co-workers also paves the way for future experiments to explore the pathological impact that the genetic alterations induced by DAMPs may have on CB function. Although the acute action of tissue injury and conditioned plasma was to elevate type I cell transmitter release, it appears that this was not well maintained and after 24 h may even have started to fall below baseline (Mkrtchian et al., 2020). Thus, the longer lasting actions of DAMPs may be to impair CB function. For instance, does the chronic up-regulation in DAMP signalling reduce CB O_2 sensitivity, potentially making individuals more susceptible to hypoxia? This could be of keen interest given that characterising the genetic and pathophysiological mechanisms underpinning individual variability/vulnerability to whole-body hypoxic exposure is a particularly hot topic at the moment due to COVID-19. Alternatively, could the DAMP-mediated genetic modifications induce persistent CB hyperactivity leading to neurogenic hypertension and arrhythmia, as observed in other conditions. Both of these possible adaptations in CB function have important clinical implications. Therefore, measuring hypoxic sensitivity in animals or patients hours or days following surgery or after traumatic tissue injury will be an important next step. In addition, exploring CB function and hypoxic sensitivity in other conditions associated with the chronic release of DAMPs such as cancer, autoimmune disorders, osteoarthritis, neurodegeneration and peripheral artery disease will also be of high interest. This could even be extended further to evaluate the impact of DAMPs on other O_2-sensitive tissues in animals and humans including pulmonary artery smooth muscle cells, known to share many similarities with the CB. Clearly this is just the beginning of this line of research, which has the potential for significant translational impact.

COMPETING INTERESTS

None

AUTHOR CONTRIBUTIONS

Sole author.

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