Damage control
Holmes, Andrew P.

DOI:
10.1113/EP088923

License:
Creative Commons: Attribution (CC BY)

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Holmes, AP 2020, 'Damage control: carotid body activation and remodelling in response to aseptic tissue injury', Experimental Physiology, vol. 105, no. 9, pp. 1467-1469. https://doi.org/10.1113/EP088923

Link to publication on Research at Birmingham portal

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.
• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
• Users may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
• Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.
Damage control: carotid body activation and remodelling in response to aseptic tissue injury

Andrew P. Holmes

Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Correspondence
Andrew P. Holmes, Institute of Clinical Sciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK
Email: a.p.holmes@bham.ac.uk

Funding information
This work was funded by a Wellcome Trust Institutional Strategic Support Fund Award to APH.

Edited by: Ken O’Halloran

Linked articles: This Viewpoint highlights an article by Mkrtchian et al. To read this paper, visit https://doi.org/10.1113/EP088705.

KEYWORDS
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 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.

ORCID
Andrew P. Holmes https://orcid.org/0000-0001-9270-9401

REFERENCES
Ackland, G. L., Kazymov, V., Marina, N., Singer, M., & Gourine, A. V. (2013). Peripheral neural detection of danger-associated and pathogen-associated molecular patterns, Critical Care Medicine, 41, e85–e92.
Holmes, A. P., Ray, C. J., Thompson, E. L., Alshehri, Z., Coney, A. M., & Kumar, P. (2019). Adrenaline activation of the carotid body: Key to CO2 and pH homeostasis in hypoglycaemia and potential pathological implications in
cardiovascular disease. Respiratory Physiology & Neurobiology, 265, 92–99.

Iturriaga, R., Moya, E. A., & Del Rio, R. (2015). Inflammation and oxidative stress during intermittent hypoxia: The impact on chemoreception. Experimental Physiology, 100, 149–155.

Mkrtchian, S., Kählin, J., Gómez-Galán, M., Ebberyd, A., Yoshitake, T., Schmidt, S., ... Eriksson, L. I. (2020). The impact of damage-associated molecular patterns on the neurotransmitter release and gene expression in the ex vivo rat carotid body. Experimental Physiology, 105, 1634–1647.

Thompson, E. L., Ray, C. J., Holmes, A. P., Pye, R. L., Wyatt, C. N., Coney, A. M., & Kumar, P. (2016). Adrenaline release evokes hyperpnoea and an increase in ventilatory CO₂ sensitivity during hypoglycaemia: A role for the carotid body. The Journal of Physiology, 594, 4439–4452.

How to cite this article: Andrew P.H. Damage control: carotid body activation and remodelling in response to aseptic tissue injury. Experimental Physiology. 2020;105:1467–1469. https://doi.org/10.1113/EP088923