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Neuroscience: Detection of systemic inflammation by the brain

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When confronted with illness, humans and animals undergo critical changes in their behavior and physiology. New research shows how neuronal circuits detect sickness and coordinate illness-specific responses.

We are all familiar with the feeling of being sick. This unpleasant state, known as sickness syndrome, can be characterized by symptoms such as fever, poor appetite, fatigue, body aches, and the urge to rest in a warm spot (like our bed). However, the complex neuronal mechanisms responsible for feeling sick are not well understood.

Activation of the immune system during inflections or body damage is the first step in a series of events that lead to the drastic physiological and behavioral alterations we typically associate with sickness. For these changes to happen, signals from the immune system must reach the central nervous system (CNS). Two mechanisms are mainly responsible for this communication: local activation of peripheral nerve endings, which, in turn, relay this information to the brain, and the release of humoral signals directly to the bloodstream. The CNS responds to these immune system-borne inputs by triggering the sickness response in an attempt to improve illness outcome[1,2].

Over the past decades, key humoral mediators involved in signaling systemic inflammation to the brain have been identified[3]. However, the specific CNS circuits responsible for sensing the pro-inflammatory state and eliciting the sickness phenotype have remained less well characterized. In a recent issue of *Nature*, Osterhout *et al.* present new data about the role of a specific group of hypothalamic neurons during sickness syndrome in mice[4]. As an entry point, the authors used the activity marker gene *Fos* to visualize those neurons that are activated as a consequence of intraperitoneal (i.p.) injection of lipopolysaccharide (LPS). LPS is part of the Gram-negative bacterial outer cell membrane. When injected, LPS can induce a robust sickness response in animals, making LPS administration a widely used experimental model to mimic bacterial infection[5].

In good agreement with previous observations[6], Osterhout *et al.* noticed that LPS induced *Fos* expression in several brain regions, including the ventral medial preoptic area (VMPO), a small hypothalamic brain region located in close proximity to the emerging third ventricle and with a known role in body temperature homeostasis[7,8] (Figure 1). The majority of LPS-activated VMPO neurons (or VMPO^{LPS}) display an inhibitory gene expression profile, suggesting these neurons are GABAergic. To some extent, VMPO^{LPS} can be differentiated from other neighboring neuronal populations by expressing the 'marker' genes *Galanin*, *Calcr*, and *Amigo2*[4]. Nevertheless, whether VMPO^{LPS} are a homogenous group of neurons expressing a defined marker gene profile remains unclear. Activation of VMPO^{LPS} in freely moving mice triggers many of the symptoms observed in sick animals, including hyperthermia, warmth seeking, and anorexia. However, activation of either Galanin- or Calcr-expressing VMPO neurons or ablation of VMPO^{LPS} can only partially explain the sickness phenotype observed during VMPO^{LPS} activation[4], arguing in favor of some molecular and functional heterogeneity within VMPO^{LPS} and the existence of other neuronal population(s) involved in sickness outside VMPO.

Furthermore, Osterhout *et al.* found VMPO^{LPS} to express receptors for pro-inflammatory cytokines, suggesting that these cells might work as direct sensors of peripheral inflammation. *In vitro* characterization showed that immune mediators with a critical role in immune–brain communication and promoting the febrile response, such as PGE_2 and IL-1[3], can indeed increase VMPO^{LPS} excitability[4].

In addition to VMPO^{LPS}, a second population of neurons has been molecularly characterized as central sensors of peripheral inflammation in mice. These cells are mainly located in the median preoptic nucleus (MnPO) of the hypothalamus, show an expression profile consistent with these neurons being excitatory and express the marker gene *Adcyap1* (henceforth referred to as MnPO$^{Vglut2/Adcyap1}$). Furthermore, ablation of MnPO$^{Vglut2/Adcyap1}$ or elimination of a specific PGE_2 receptor from the MnPO (and adjacent areas) renders mice unable to mount a fever response upon LPS injection, strongly supporting a role of MnPO$^{Vglut2/Adcyap1}$ in both direct detection of PGE_2 and LPS-mediated fever[9,10]. Besides inflammatory fever, MnPO$^{Vglut2/Adcyap1}$ are also activated by warm environmental conditions, and stimulation of MnPO$^{Vglut2/Adcyap1}$ promotes body cooling[11–14].

The anatomical proximity of VMPO^{LPS} and MnPO$^{Vglut2/Adcyap1}$ (Figure 1), their disparate neurochemistry (with one population being inhibitory and the other excitatory) and their shared ability to detect inflammatory mediators are intriguing and raise the question of whether VMPO^{LPS} and MnPO$^{Vglut2/Adcyap1}$ could form a local circuit involved in regulating the fever response. In this regard,

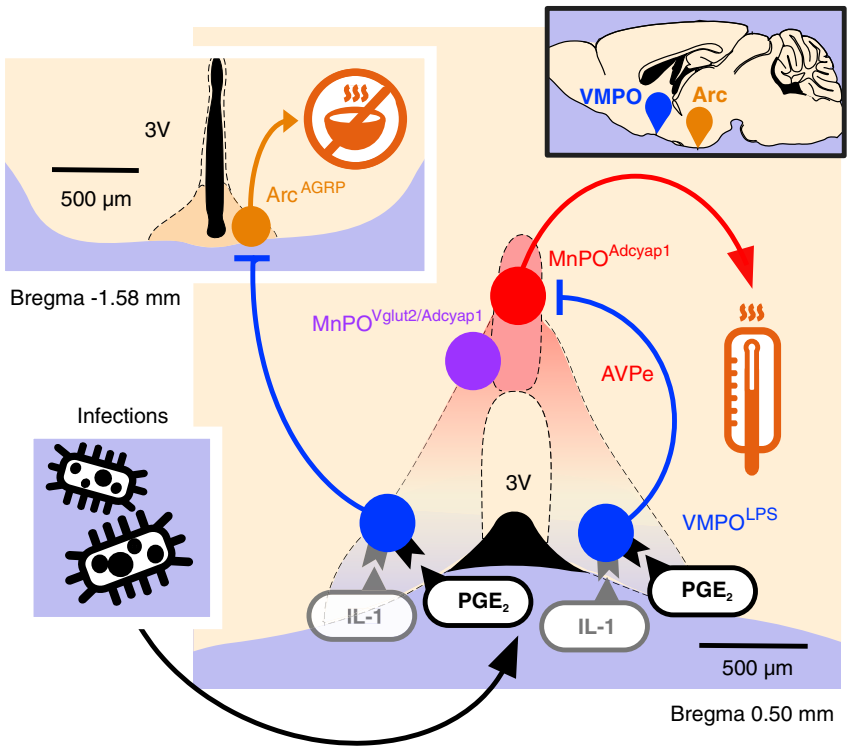

Figure 1. Detecting inflammation in the brain.
Infections trigger the production of inflammatory mediators such as PGE2 and IL-1 (black and grey bubbles, respectively). LPS-activated VMPO neurons ($VMPO^{LPS}$, blue) detect these mediators and inhibit downstream body-cooling $MnPO^{Adcyap1}$ (red) and hunger-promoting Arc^{AGRP} (orange) neurons to induce fever and anorexia. Mouse brain schemes modified from[15]. AVPe, anteroventral periventricular nucleus; 3V, third ventricle; Arc, arcuate nucleus.

Osterhout *et al.* found that $VMPO^{LPS}$ innervate different brain nuclei, including many with known roles in temperature, energy, and sleep homeostasis. Among those nuclei, some $VMPO^{LPS}$ connect to adjacent neurons in the MnPO and form direct synaptic connections with warm-responding Adcyap1-expressing MnPO neurons ($MnPO^{Adcyap1}$). Activation of $VMPO^{LPS}$ terminals innervating $MnPO^{Adcyap1}$ increases body temperature without altering food consumption. These observations prompted Osterhout *et al.* to propose that direct and/or indirect cytokine-activation of $VMPO^{LPS}$ promotes inhibition of $MnPO^{Adcyap1}$. In turn, reduced activity of $MnPO^{Adcyap1}$ facilitates fever by inhibiting heat-dissipation and enhancing heat-conservation thermoregulatory mechanisms[4] (Figure 1).

Although the $VMPO^{LPS}$–$MnPO^{Adcyap1}$ hypothesis of fever generation is very attractive, the immediate vicinity of $VMPO^{LPS}$ and $MnPO^{Adcyap1}$ poses methodological challenges to assess the role of this circuit *in vivo*. Despite this, further evidence supporting a role of $MnPO^{Adcyap1}$ inhibition in fever generation exists. For instance, inhibition of a subgroup of Adcyap1-expressing MnPO neurons promotes hyperthermia[14]. Additionally, a proportion of Adcyap1-positive MnPO neurons expresses an inhibitory PGE_2 receptor[9], suggesting that inflammatory conditions might promote $MnPO^{Adcyap1}$ inhibition directly and independently of $VMPO^{LPS}$.

In addition to the $VMPO^{LPS}$–$MnPO^{Adcyap1}$ connection, Osterhout *et al.* found that a fraction of $VMPO^{LPS}$ project to the arcuate nucleus of the hypothalamus (Arc), a critical brain center for energy homeostasis and appetite control. In the Arc, $VMPO^{LPS}$ innervate hunger-activated AGRP-expressing neurons (or Arc^{AGRP}). Furthermore, direct activation of Arc-targeting $VMPO^{LPS}$ nerve endings produces a drastic reduction in food consumption in mice while body temperature remains unaltered (Figure 1). These findings suggest that, during sickness, $VMPO^{LPS}$ decrease appetite by inhibiting hunger-promoting Arc^{AGRP}.

Collectively, Osterhout *et al.* describe an anatomically defined group of neurons in the hypothalamus that can sense inflammatory conditions and that can coordinate multiple physiological and behavioral sickness responses by recruiting discrete downstream brain regions[4]. We expect future studies to further elucidate the specific contribution of (local) $VMPO^{LPS}$ circuitry — and its interaction with neighboring non-neuronal cells that release cytokines locally — to sickness syndrome generation. New and refined experimental tools to precisely monitor, manipulate and control local circuit activity and release of inflammatory mediators *in vivo* will be required to accomplish this goal.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Konsman, J.P., Parnet, P., and Dantzer, R. (2002). Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. *25*, 154–159.

2. Hart, B.L. (1988). Biological basis of the behavior of sick animals. Neurosci. Biobehav. Rev. *12*, 123–137.

3. Blomqvist, A., and Engblom, D. (2018). Neural mechanisms of inflammation-induced fever. Neuroscientist *24*, 381–399.

4. Osterhout, J.A., Kapoor, V., Eichhorn, S.W., Vaughn, E., Moore, J.D., Liu, D., Lee, D., DeNardo, L.A., Luo, L., Zhuang, X., and Dulac, C. (2022). A preoptic neuronal population controls fever and appetite during sickness. Nature, https://doi.org/10.1038/s41586-022-04793-z.

5. Lasselin, J., Schedlowski, M., Karshikoff, B., Engler, H., Lekander, M., and Konsman, J.P. (2020). Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: relevance for symptoms of anxiety and depression. Neurosci. Biobehav. Rev. *115*, 15–24.

6. Dallaporta, M., Pecchi, E., Jacques, C., Berenbaum, F., Jean, A., Thirion, S., and Troadec, J.D. (2007). c-Fos immunoreactivity induced by intraperitoneal LPS administration is reduced in the brain of mice lacking the microsomal prostaglandin E synthase-1 (mPGES-1). Brain Behav. Immun. *21*, 1109–1121.

7. Tan, C.L., Cooke, E.K., Leib, D.E., Lin, Y.C., Daly, G.E., Zimmerman, C.A., and Knight, Z.A. (2016). Warm-sensitive neurons that control body temperature. Cell *167*, 47–59.

8. Pinol, R.A., Mogul, A.S., Hadley, C.K., Saha, A., Li, C., Skop, V., Province, H.S., Xiao, C., Gavrilova, O., Krashes, M.J., *et al*. (2021). Preoptic BRS3 neurons increase body temperature and heart rate via multiple pathways. Cell Metab. *33*, 1389–1403.

9. Machado, N.L.S., Bandaru, S.S., Abbott, S.B.G., and Saper, C.B. (2020). EP3R-expressing glutamatergic preoptic neurons mediate inflammatory fever. J. Neurosci. *40*, 2573–2588.

10. Lazarus, M., Yoshida, K., Coppari, R., Bass, C.E., Mochizuki, T., Lowell, B.B., and Saper, C.B. (2007). EP3 prostaglandin receptors in the median preoptic nucleus are critical for fever responses. Nat. Neurosci. *10*, 1131–1133.

11. Abbott, S.B.G., and Saper, C.B. (2017). Median preoptic glutamatergic neurons promote thermoregulatory heat loss and water consumption in mice. J. Physiol. *595*, 6569–6583.

12. Yu, S., Qualls-Creekmore, E., Rezai-Zadeh, K., Jiang, Y., Berthoud, H.R., Morrison, C.D., Derbenev, A.V., Zsombok, A., and Munzberg, H. (2016). Glutamatergic preoptic area neurons that express leptin receptors drive temperature-dependent body weight homeostasis. J. Neurosci. *36*, 5034–5046.

13. Harding, E.C., Yu, X., Miao, A., Andrews, N., Ma, Y., Ye, Z., Lignos, L., Miracca, G., Ba, W., Yustos, R., *et al*. (2018). A neuronal hub binding sleep initiation and body cooling in response to a warm external stimulus. Curr. Biol. *28*, 2263–2273.

14. Zhang, K.X., D'Souza, S., Upton, B.A., Kernodle, S., Vemaraju, S., Nayak, G., Gaitonde, K.D., Holt, A.L., Linne, C.D., Smith, A.N., *et al*. (2020). Violet-light suppression of thermogenesis by opsin 5 hypothalamic neurons. Nature *585*, 420–425.

15. Paxinos, G., and Franklin, K.B.J. (2001). The Mouse Brain in Stereotaxic Coordinates, 2nd Edition (San Diego: Academic Press).

Aging: Lifespan and the evolution of somatic mutation rates

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A new study finds an inverse correlation between lifespan and somatic mutation rate in mammals. This suggests an evolutionary relationship between aging and somatic mutation rates, perhaps mediated by selection against noncancerous selfish lineages.

Death and taxes are famously quoted as the only certainties in life, but of course there are others. Among these are the accumulation of mutations in the somatic cells of multicellular organisms, and (for those who live long enough) the senescent decline in function that accompanies old age. In 1959, Leo Szilard[1] proposed that the latter two certainties are intertwined: namely, that age-related senescence (or simply, 'aging') arises as a consequence of continued somatic cell death due to mutation. There has been little empirical support for Szilard's relatively simple idea, and given the recessive nature of most loss-of-function mutations and what is now known of the scale of somatic mutation rates, somatic mutation seems unlikely to be a major contributor to aging in the way he envisioned. Nonetheless, somatic mutation clearly could have something to do with aging: cancer, for example, arises as a consequence of intra-organismal selection on somatic mutations, and the longer an organism lives the more likely it is to have suffered such mutations. Writing recently in *Nature*, Cagan, Baez-Ortega *et al.*[2] provide a novel perspective on aging and somatic mutation, showing that somatic mutation rates correlate inversely with lifespan in mammals and suggesting that selection against the generation of selfish cell lineages (though, interestingly, not cancers) is the most likely evolutionary driver of this intriguing relationship.

Both the evolutionary forces that produce aging and its proximate cellular and molecular causes have long been of interest to biologists. Imagine a species that is intrinsically immortal, but for which extrinsic mortality (from, e.g., accidents or random predation events) is 10% per year. Although members of such a species would be perfectly capable of living to an age of 130 years, only one in a million will be lucky enough to do so. A mutant allele causing intrinsic mortality at about this age is thus effectively invisible to selection; because mutation is unavoidable, such alleles will accumulate in the population, causing the evolution of aging. This elegant reasoning was presented by Medawar[3] and was complemented by Williams[4], who pointed out that the situation is even worse: natural selection will actually *favor* mutations that increase fitness early in life and decrease it late in life, because there are far more young than very old individuals alive in a population at any given time.

These evolutionary theories show why we should expect aging to occur, but they do not address its mechanistic causes. Given the complexity of eukaryotic multicellular biology, we might expect aging to result from many proximate causes, all of which tend to manifest at about the same time[5]. Indeed, the known cellular and molecular causes of aging are legion[6], such that there probably is no master regulator or central process of aging[7]. For example, mice with enhanced telomerase function live longer, but only if they are simultaneously enhanced for cancer resistance[8]. In this respect, to the