INNATE IMMUNITY

The stress connection

Smoking and prolonged stress have been linked to increased susceptibility to bacterial infection. New research in *Cell Host and Microbe* now shows that this may be caused by a decrease in antimicrobial peptide (AMP) activity as a result of increased stimulation of a neuroendocrine signalling pathway.

AMPs such as cathelicidin are present in the skin and mucous membranes and constitute an important first line of innate immune defence. These abundant small molecules not only have direct and indirect antibacterial activity, but they also fulfil important immunomodulatory functions. It has previously been shown that smoking can increase susceptibility to skin and lung infections and that exposure to psychological stress can decrease AMP production in the skin of mice. Katherine Radek and colleagues wanted to investigate the role of the neuroendocrine system in the negative regulation of AMP production, looking specifically at cholinergic stimulation of nicotinic acetylcholine receptors (nAChRs).

To evaluate the effects of nicotine on AMP production, mice were treated topically with nicotine and AMPs were then extracted from the skin. Functional analysis showed that nicotine treatment reduced AMP activity. Furthermore, AMPs extracted from the skin of chromogranin A (CHGA)-deficient (*Chga*$^{-/-}$) mice, which lack the endogenous nAChR antagonist catestatin (a derivative of CHGA), showed reduced antibacterial activity. Full AMP activity could be restored by topical application of a nAChR antagonist. Further work showed that *Chga*$^{-/-}$ mice were more susceptible to intradermal challenge with methicillin-resistant *Staphylococcus aureus* and group A *Streptococcus* (GAS) than wild-type mice, having larger necrotic skin lesions and a greater bacterial burden. The authors went on to investigate the effects of stress and found that wild-type mice that had been subjected to psychological stress were more susceptible to infection with GAS than control mice, but this phenotype was not seen in *Chga*$^{-/-}$ mice. Finally, the effects of GAS infection on AMP gene expression in *Chga*$^{-/-}$ mice were investigated, and cathelicidin and β-defensins were found to be downregulated.

So, increased stimulation of nAChRs by exposure to nicotine or stress might suppress the innate immune response to infection by reducing AMP activity. This is consistent with previous research showing that smoking and stress can both lead to an increased susceptibility to infection.

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