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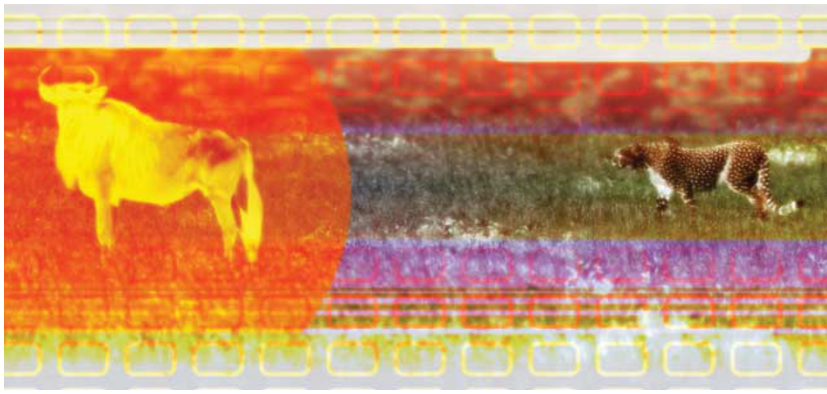
RESPIRATORY DISEASE

Timing is everything



Remarkable though it might seem, data published recently in *Proceedings of the National Academy of Sciences* indicate that beta-blockers (β-adrenoceptor antagonists or inverse agonists), which are presently contraindicated for asthmatics, might actually be able to prevent serious attacks.

In asthma patients, excessive sensitivity of the airways to various stimuli leads to airway narrowing that can cause respiratory failure or even death. The standard cure for an attack is the acute administration of β_2-agonist 'bronchodilators', which bind to β_2-adrenoceptors lining the bronchial tubes and prevent the muscle contraction that hampers the flow of air to and from the lungs. However, recent clinical trials have shown that chronic administration of these drugs can have detrimental effects, even increasing the risk of death.

Richard Bond and colleagues proposed that duration of therapy might be a key determinant of whether β-adrenoceptor ligands have a positive or negative effect. They suggested that beta-blockers, which have been shown to be harmful to asthmatics in the short term, might actually have beneficial effects when administered long term.

To investigate this hypothesis, airway sensitivity to methacholine — which elicits airway narrowing — was monitored in mouse models of asthma after chronic (daily dosing over 28 days) and acute (single dose, 15 minutes before methacholine administration) administration of a range of β_2-ligands: salbutamol (a partial β_2-agonist), alprenolol (a β_1/β_2-antagonist with partial β_2-agonist activity), carvedilol and nadolol (both β_1/β_2-antagonists with inverse agonist activity at the β_2-adrenoceptor). As expected, acute administration of salbutamol decreased airway responsiveness to methacholine compared with non-treated asthmatic mice, whereas chronic dosing had no effect. Similar results were observed for alprenolol, indicating that it was behaving as a β_2-agonist. Carvedilol and nadolol, on the other hand, although acutely detrimental, significantly reduced airway sensitivity after chronic administration.

The researchers then used radioligand-binding assays to examine β-adrenoceptor density in mouse lungs. They found the density of β-adrenoceptors to be significantly lower in asthmatic mice compared with controls, and then showed that the capacity to reduce airway responsiveness in asthmatic mice correlated with a ligand's ability to increase β-adrenoceptor density. Salbutamol and alprenolol increased β-adrenoceptor density in the lungs after an acute dose but had no effect after chronic administration, whereas carvedilol and nadolol had no acute effect, but significantly increased β-adrenoceptor levels with chronic dosing.

So, it seems that chronic occupation of β_2-adrenoceptors by beta-blockers can evoke a compensatory response, in which receptor numbers are upregulated, resulting in enhanced bronchoprotection. Whether these results will extrapolate to humans remains to be shown, but this is not the first time that such a therapeutic paradox has come to light. Until the late 1990s, all beta-blockers were contraindicated for patients with congestive heart failure, yet some beta-blockers are now a key part of first-line therapy for this disease. Perhaps, say the authors, it might be worth looking for paradoxical approaches to treating other chronic diseases, as potential therapies might have been missed through failure to monitor long-term effects. Of course, if successful, such approaches would no longer be 'paradoxical'.

Clare Ellis

References and links

ORIGINAL RESEARCH PAPER Callaerts-Vegh, Z. *et al.* Effects of acute and chronic administration of β-adrenoceptor ligands on airway function in a murine model of asthma. *Proc. Natl Acad. Sci. USA* **101**, 4948–4953 (2004)