Haemorrhagic shock: endogenous cannabinoids to the rescue

Activation of peripheral CB1 cannabinoid receptors in haemorrhagic shock

Wagner, J.A. *et al.* (1997)

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Massive blood loss following injury initiates a series of events that include prolonged hypotension. This unique response apparently evolved to minimize tissue damage by inducing vasodilation, allowing reduced amounts of available blood to support the most vital functions. Hypotension also minimizes blood loss while the clotting system springs into action. Previous studies have implicated nitric oxide (NO), the major endogenous vasodilator, in this function. This new study implicates increased synthesis and release of endogenous cannabinoids by activated macrophages in haemorrhagic shock hypotension. Hypotension was induced by slowly bleeding rats until their blood pressure dropped from 120 mm Hg to 40 mm Hg. Blood pressure remained stable at this level for about 30 min, when it declined and the animals died. The study demonstrated that when 3 ml heparinized blood from 'shocked' animals was transfused to recipient rats, it induced a strong (33 mm Hg) hypotensive response lasting over 2 h. Blood from control donors had no effect on the blood pressure of recipient animals. Testing different blood components indicated that macrophages or platelets, but not plasma or lymphocytes, could transmit this hypotensive response. Further experimentation showed that macrophages from shocked animals produced increased amounts of the endogenous cannabinoid anandamide (arachidonylethanolamine), and that the hypotensive response in both 'shocked' and recipient animals could be effectively blocked by the potent CB1 cannabinoid receptor antagonist SR141716A.

Interestingly, blocking haemorrhagic shock hypotension by pretreating the animals with this cannabinoid antagonist strongly reduced their survival time (from mean values of about 30 min to merely 8 min). In contrast, pretreatment with tetrahydrocannabinol (THC), the major active ingredient of marijuana, nearly doubled their survival time, clearly illustrating the physiological importance of cannabinoids in haemorrhagic shock, and indicating that pharmacological activation of peripheral CB1 cannabinoid receptors could further sustain survival. It was suggested that cannabinoids might induce hypotension via specific CB1 receptors located on vascular smooth muscle cells. Clarifying just how endogenous (and exogenous) cannabinoids mediate haemorrhagic shock hypotension has profound practical implications for emergency medicine. Just imagine how many more car accident victims would have a chance to survive if emergency services would have double the time to get them alive to the operating table.

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Vaccine evasion by pneumococci: as easy as changing a cassette

Recombinational exchanges at the capsular polysaccharide biosynthetic locus lead to frequent serotype changes among natural isolates of *Streptococcus pneumoniae*

Coffey, T.J. *et al.* (1998)

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Clinical isolates of *Streptococcus pneumoniae*, a cause of human pneumonia and meningitis, are becoming increasingly resistant to antimicrobials. The pneumococcal capsule is required for virulence, and vaccines directed to the capsule protect healthy adults. However, 90 pneumococcal serotypes have been described, each of which has an individual capsule structure. A vaccine consisting of purified capsular polysaccharide from 23 serotypes associated with invasive disease has poor efficacy in high-risk groups, such as infants. New conjugate vaccines directed at eight of the major serotypes are being developed.

The capsular biosynthetic genes in pneumococci are clustered on a large chromosomal locus called *cps*. The *cps* loci from different serotypes are quite distinct, but are flanked by conserved genes forming a cassette-like structure. Coffey *et al.* studied eight variant strains of the serotype-19F group isolated from Spanish hospitals. They were found to be virtually identical to the common Spanish multiresistant serotype-23F clone, but have a large recombinant replacement in the *cps* locus. Two of the cross-over points were internal to the *cps* locus, and sequence data suggested that the variation arose via transformation and recombination. Of the eight variant strains studied, at least four had unique cross-over points, suggesting that recombination between the two serotype groups has occurred on at least four separate occasions. The Spanish serotype 23F is thought to be about 20 years old, so changes in capsular type by recombination appear to occur in nature relatively frequently. In fact, genetic transformation was first described in pneumococci, and they are known to have inefficient mechanisms for the prevention of interspecies recombination.

This paper demonstrates the significant potential for pathogenic pneumococci to acquire capsule loci from other strains or species (some of which are not usually associated with disease), thereby evading the protection afforded by current vaccines. The vaccines might even be applying selective pressure. Futhermore, it raises the possibility of new serotypes emerging from partial replacement of the *cps* locus. This would reduce the ability of pneumococcal vaccines – including the newly developed ones – to control pneumococcal infection, and would make the design of vaccines in the future even more challenging.

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