Sic in epidemic waves of GAS

Group A streptococci (GAS) cause 'strep throat' and, occasionally, invasive diseases such as rheumatic fever and necrotizing fasciitis (flesh-eating disease). In several continents, epidemic outbreaks of GAS disease lasting 1–3 years have been observed, and it has been assumed that one (or a few) particularly 'fit' strains are responsible. However, a possible cause of increased fitness or host resistance in epidemic strains does not appear to be associated with obvious GAS virulence genes, and the reason for these outbreaks had remained a mystery. Musser and colleagues[1,2] have now suggested a new hypothesis for the development of epidemic waves of GAS infection, which includes a role for the *sic* gene (streptococcal inhibitor of complement).

The sequence of the *sic* gene, in strains that had been isolated during several epidemics, showed it to be highly polymorphic. Mutations predominantly led to amino acid changes or radical replacements, whereas synonymous changes were rarer. Furthermore, many of the mutations represented single-event changes from other isolates of the same epidemic. Armed with these observations, they have now shown that: (1) a GAS-strain constructed with a *sic* deletion colonized the mouse throat less efficiently than the wild-type strain[2]; (2) mice and humans produce antibodies directed towards the Sic protein[2]; (3) mutant forms of Sic protein inhibit complement[1]; and (4) in a mouse throat-infection model, only 1% of GAS show *sic* mutations at 45 days, whereas, at 54 days, 74% of GAS have *sic* mutations. *sic* mutations are rare *in vitro*, suggesting that variation is selected for in the throat[1] – after sufficient time for an anti-Sic response to be generated.

These results suggest that the Sic protein is necessary for efficient colonization, that infected hosts produce antibodies to this protein, and that GAS strains that produce variant, but functional, Sic proteins have a selective advantage in the throat. It is envisaged that these mutants then infect new hosts during the epidemic, and further mutants are selected. Therefore, these epidemic waves of GAS disease appear to result from a highly heterogeneous population of strains that are evolving by rapid natural selection to evade the human humoral response.

1 Hoe, N.P. *et al.* (1999) Rapid selection of complement-inhibiting protein variants in group A *Streptococcus* epidemic waves. *Nat. Med.* 5, 924–929

2 Lukomski, S. *et al.* (2000) Nonpolar inactivation of the hypervariable streptococcal inhibitor of complement gene (*sic*) in serotype M1 *Streptococcus pyogenes* significantly decreases mouse mucosal colonization. *Infect. Immun.* 68, 535–542

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Renewed hope for medicinal marijuana?

The public debate for and against the approval of medicinal cannabis use could intensify following a study by Baker *et al.*[1] implying that cannabinoids could potentially ease the motor symptoms of multiple sclerosis (MS) patients. The study employed an animal model of MS – chronic relapsing experimental allergic encephalomyelitis (CREAE). In this model, Biozzi ABH mice are injected with mouse spinal-cord homogenate in Freund's complete adjuvant (a water-in-oil emulsion used to stimulate a vigorous response to the homogenate). After 2–3 weeks, the mice develop an acute paralysis phase, followed by relapse typically occurring around one month post-injection, later followed by alternating remission and relapse periods. The remission periods are characterized by hindlimb spasticity and tremor, and resemble the chronic relapsing motor symptoms observed in MS patients.

MS is a progressive autoimmune disorder in which the immune system attacks and destroys the myelin that surrounds motor neurons. It has been proposed that marijuana or synthetic cannabinoids, known for their immunosuppressive potency, might be employed for treating autoimmune disorders such as MS. Anecdotal reports of the beneficial effects of marijuana-smoking in MS patients were often publicized. A previous study, which anonymously surveyed MS patients, reported that cannabis improved spasticity in over 90% of cases[2]. However, no controlled trials comparing the usefulness of cannabinoids with currently available therapies for spasticity in MS had been reported.

This new study shows that cannabinoids, notably Δ^9-tetrahydrocannabinol (the major active ingredient of cannabis), and the synthetic agonists methanandamide and WIN 55,212 dramatically reduce motor dysfunction symptoms in CREAE mice. Pharmacological evaluation indicates that both CB1 and CB2 brain cannabinoid-receptor subtypes are implicated in the improved motor function, although the brain CB1 subtype predominates. The improvements in spasticity and tremor occur within a few minutes and last for a few hours, which excludes immune suppression as the mechanism for these beneficial effects. The cannabinoid antagonists SR141716A and SR144528 increase spasticity in CREAE mice, indicating that endogenously produced cannabinoids, such as anandamide, inherently reduce motor symptoms in these animals.

The study provides a rationale for carefully-designed controlled clinical trials of cannabinoid drugs for relieving tremor and spasticity in MS patients. The authors caution, however, that it might be difficult to dissociate the beneficial motor effects from the undesired psychoactive effects of cannabinoids, also mediated via brain CB1 receptors. Maybe a safer clinical approach should aim at elevating the levels of endogenous brain cannabinoids by inhibiting fatty acid amide hydrolase, the anandamide catabolic enzyme. Questions remain over the relevance of these new observations for other motor disorders such as Parkinson's disease and Tourette syndrome.

1 Baker, D. *et al.* (2000) Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 404, 84–87

2 Consroe, P. *et al.* (1997) The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur. Neurol.* 38, 44–48

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