Marijuana: a tumour growth promoter?

A major constituent of marijuana smoke, Δ-9-tetrahydrocannabinol (THC), suppresses the immune system and promotes tumour growth, according to a recent study carried out at the University of Los Angeles and the Veterans Affairs West Los Angeles Healthcare Center (Los Angeles, CA, USA)[1]. THC is known to suppress macrophages, natural killer cells and T-lymphocytes[2–4], and reduce resistance to viral and bacterial infections[5,6], but this is the first time that it has been shown to enhance tumour growth.

The research team, led by Steven Dubinett (UCLA School of Medicine, Los Angeles, CA, USA), found that THC promoted tumour growth in two immunocompetent mouse lung cancer models. However, it did not affect tumour growth in immunocompromised mice (Fig. 1), suggesting an immune-mediated response to the cannabinoid.

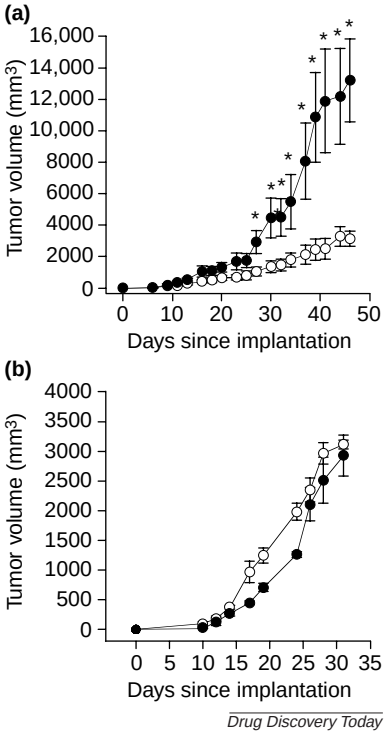

Figure 1. *BALB/c or C57BL/6 mice were treated with Δ-9-tetrahydrocannabinol (THC) for 2 weeks before receiving implants of cells from one of two lung tumour cell lines [Lewis Lung carcinoma (3LL) or line 1 alveolar carcinoma (LIC2, illustrated)]. THC enhanced tumour growth in both the BALB/c (a) and C57BL/6 models. However, THC had no effect on tumour growth in immunodeficient mice [severe combined immunodeficiency BALB/c mice, (b)][1]. *$P<0.01$ compared with diluent control treated mice. [Reproduced with permission from* The Journal of Immunology*]. Key: diluent control (open circles); 5 mg kg^{-1} THC (closed circles).*

THC mechanism

The release of cytokines by T cells is central to the immune and anti-tumour responses. Type-1 cytokines, including interleukin-2 (IL-2) and interferon-γ (IFN-γ), activate cell-meditated immunity and the anti-tumour response, while type-2 cytokines, such as IL-10 and tumour growth factor-β (TGF-β), inhibit the response. In the models used by the UCLA team, THC upregulated the inhibitory cytokines IL-10 and TGF-β and downregulated the activating cyto-kine IFN-γ in both lung and spleen tissue. Tumour growth in response to THC was also inhibited by anti-IL-10 and anti-TGF-β antibodies.

The researchers postulated that THC probably interacts with the T-cell cannabinoid CB_2 receptor to produce these effects. Unlike the CB_1 receptor, which is mostly found in the CNS, the CB_2 receptor is expressed predominantly in immune cells[6]. Indeed, the team later found that a specific CB_2-receptor antagonist inhibited THC-evoked enhancement of tumour growth. Moreover, says Dubinett, 'It seems likely that endogenous cannabinoids also interact with immune cells via this receptor and could play a role in modulation of the immune system. Therefore, drugs that block this interaction might be useful as anticancer agents. By contrast, those that stimulate the receptor might be used to suppress the immune system in people undergoing transplantation.' He adds, 'We are currently looking at the interaction between the CB_2-receptor modulation and TGF-β in human lymphocytes and we also plan to look at potential therapeutic agents that act by blocking the CB_2 receptor, thereby suppressing immunity.'

Implications for marijuana smokers

The UCLA finding supports epidemiological evidence of an increased risk of cancer among marijuana smokers. 'There is anecdotal evidence for an increased risk of head and neck cancers in marijuana smokers and large-scale epidemiological studies are currently going on to confirm this,' explains Dubinett. 'There is also a suggestion in the literature that marijuana might contribute to a poor outcome in people with HIV infection, although this also has yet to be confirmed,' he adds.

'The blood levels reached in the mice in our experiments are thought to be comparable to those reached in people who smoke marijuana, although it is difficult to say so precisely,' says

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Dubinett. Also, while the researchers do not know how long the effect of THC lasts in the body, they believe that it probably has a cumulative effect and, like cigarette smoking, might decline when people stop smoking marijuana. 'THC interacts with specific receptors on immune cells and causes a specific immune effect. Therefore, the chances are that if people stop smoking marijuana, they will probably reduce their risk of cancer,' speculates Dubinett.

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Antibiotics: a possible treatment for regressive-onset autism

A new study has added further weight to speculation that autism might be linked to abnormalities of the bowel, at least in a subset of affected children. The study, conducted at the Rush-Presbyterian-St Luke's Medical Center in Chicago (IL, USA), reports significant short-term improvements with vancomycin treatment in a group of autistic children whose symptoms appeared after they developed chronic diarrhoea from treatment with broad-spectrum antibiotics[1].

Autism: the disease

Autism is a devastating, pervasive developmental disorder that usually manifests itself in early infancy. Autistic children lack social and language skills, exhibit repetitive behaviours and are unable to form normal relationships. The cause is unknown, but a US National Institutes of Health working group in 1995 cited a probable genetic susceptibility involving multiple, unidentified genes[2]. However, various studies have suggested a possible link with bowel abnormalities such as abnormal permeability and ileal-lymphoid nodular hyperplasia[3,4].

About one-third of cases are classified as regressive-onset, with the child appearing to develop normally for the first 1–2 years and then losing previously acquired skills. This happened to the son of Ellen Bolte, a co-author of the Rush-Presbyterian-St Luke's study. At 17 months, he developed chronic diarrhoea after three 10-day courses of various broad-spectrum antibiotics given for a middle ear infection. At 19 months, his behaviour and development deteriorated profoundly and he developed severe autistic features. Extensive testing revealed no discernible cause for his condition. Bolte developed the hypothesis that broad-spectrum antibiotics might disrupt the normal intestinal flora, enabling the growth of neurotoxin-producing bacteria[5]. These neurotoxins, she speculated, could cause the symptoms of autism.

She took the theory to Richard Sandler, director of paediatric gastroenterology at Rush Children's Hospital. Although sceptical, he agreed to treat the boy with vancomycin. After 2–3 weeks, he showed a rapid and dramatic improvement in his behavioural, social and language skills, and a reduction in repetitive and self-stimulatory behaviour. Unfortunately he deteriorated shortly after treatment ended.

Trial results

To see if the effect could be replicated, Sandler and colleagues set up an open-label trial with 11 children aged 43–84 months[1]. All had a definable, rapid onset of autistic symptoms after 12 months of age, two months or less after a course of antibiotics, and a persistent history of diarrhoea that had started before autism became apparent. They were given a baseline evaluation using a recognized developmental profile and the Child Autism Rating Scale; six were classified as having severe autism, two moderate and three mild. They were also videotaped at baseline and during therapy, and their taped activity was scored by a clinical child psychologist using criteria relating to behaviour, communication and social skills. Behaviour and communication were also rated by the study doctor at baseline, during therapy and at follow-up. They were given vancomycin at 500 mg day^{-1} for 8 weeks.

Eight showed an improvement in their videotape scores during treatment, and there was a statistically significant improvement in communication and behaviour scores for the group as a whole. In some cases, the improvements were impressive. However, all

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