Cannabis effects and therapeutic cues: The “Munchies”

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Abstract: In this article, the phenomenon known as the ‘Munchies’ is explored. The internal mechanisms of the human physiology which govern appetite and hunger are briefly explained. How these internal mechanisms are interrelated with the endocannabinoid system, and more specifically the CB1 receptor, are described. Pharmacological efforts targeting the CB1 receptor are discussed, along with their implications for future research targeting this receptor. Finally, the case for use of active compounds derived from cannabis, and their therapeutic applications for specific diseases is hypothesized.

Keywords: munchies, appetite, hunger, cannabinoids, rimonabant, Δ⁹-tetrahydrocannabinol, cannabidiol, Δ⁹-tetrahydrocannabivarin

The ‘Munchies’, a term well associated with the insatiable desire to eat when under the influence of Cannabis, is caused by a various array of physiological events which lead to the stimulation of hunger. This is accompanied by, and often preceded by, feelings of euphoria as a result of the activation of certain cannabinoid receptors. Studying the ‘Munchies’ effect has developed a greater deal of understanding in the role of the endocannabinoid system (ECS) and appetite stimulation. However much still remains a mystery in this area. Further investigation of the intricate interplay between various cellular signalling pathways could be the key to finding novel ways to treat various eating disorders such as anorexia, cachexia and obesity; as various studies have implicated the role of the ECS in the aforementioned diseases (Marco et al., 2012).

It is widely accepted that the smell of food causes the stimulation of appetite (Rolls, 2005). Agonism or stimulation of the CB1 receptor dampens the effect of the negative feedback system present in the olfactory cortex, and this double negative effect leads to an enhanced sense of smell (Soria-Gómez et al., 2014). Therefore, people experiencing the ‘high’ have an augmented sensory response to odour, and tend to have a higher appreciation of food than usual. This olfactory pathway is presently being used to give appetite suppressing effects through an aromatherapy technique that involves the smelling of a strong fragrance (such as Vanilla or grapefruit) for more than five minutes, to magnify the negative feedback loop on the olfactory bulb.
Cannabis has been shown to have its effect on appetite mainly through the CB$_1$ receptor. The CB$_1$ receptor has been implicated in the olfactory system that triggers smell, but is also involved in the neuronal signalling that triggers the sense of hunger and satiety (Palouzier-Paulignan et al., 2012). Therefore, it can be a key regulator in modulating appetite.

The arcuate nucleus is the critical centre of appetite control in the hypothalamus, which integrates signals from the brainstem and the periphery (Minor et al., 2009). The two main neuronal populations controlling appetite are the NPY/AGRP (orexigenic) and the POMC/CART neurons (anorexigenic), which are stimulated by a variety of signals which indicate hunger or satiety.

However recent research has shed new light on the role of the POMC/CART neurons. Coincidently, it was a study which looked at the activity of these neurons when feeding was induced with CB$_1$ stimulation. This revealed a very interesting characteristic about them. It was discovered that upon CB$_1$ activation, a mitochondrial protein caused the POMC/CART neurons to switch from giving an anorexigenic signal to giving an orexigenic one to downstream effector neurons (Koch et al., 2015). This contrasting finding points to just some revelations that can be made in this area, and could reveal more targets for therapeutic intervention.

The two key peptides that are part of the orexigenic and anorexigenic pathways are Ghrelin and Leptin (Klok et al., 2007). Ghrelin is a peptide released by the ghrelinergic cells of the stomach when it is empty, and the release of this peptide is stopped when the stomach is stretched. Ghrelin is one of the peptides responsible for stimulating hunger in the body, and
CB1 activation has been shown to increase the release of Ghrelin (Zbucki et al., 2008). Overeating and not feeling ‘full’ after copious amounts of food is often a prominent feature of the “Munchies”. This could possibly be caused by the increased release of Ghrelin, but this feature hasn’t yet been investigated.

Leptin is a peptide produced by adipose tissue and acts on the arcuate nucleus of the hypothalamus in the brain to suppress hunger (Brennan and Mantzoros, 2006). The ‘Leptin’ name was appropriately derived from the Greek word ‘Leptos’, meaning thin. Studies have shown that CB1 agonism counteracts the effects of Leptin in Hypothalamus (Palomba et al., 2015). In anorexia nervosa, leptin levels are usually higher than normal (Frederich et al., 2002). On the other hand in anorexia-cachexia syndrome, leptin levels are usually decreased and appetite suppression is caused by inflammatory mediators which activate anorexigenic signals from the POMC/CART neurons (Frederich et al., 2002). However, there is still much ambiguity concerning the relationship of cannabis and Leptin, as a pilot study investigating the effects of cannabis on HIV-infected men showed increases in Leptin in the blood plasma (Riggs et al., 2012). Further clarification on the regulation of Leptin and its consequent appetite control, possibly through cannabinoid induced feeding studies, could provide newer and more effective ways to treat various eating disorders.

With the discovery of the CB1 receptor’s role in in appetite control and eating disorders (Kirkham and Tucci, 2006)-drugs have been developed to target it. Rimonabant, a CB1 antagonist, blocks the CB1 centrally as well as in the periphery. Although it has shown to be efficacious in treating obesity, it’s psychiatric adverse effects prevented it’s approval (Moreira and Crippa, 2009). Opinions concerning Rimonabant (and blocking the CB1 receptor) within the scientific and medical community vary significantly. Some pharmacologists claim that Rimonabant has a strong antagonising ability because it is an inverse agonist (Tai et al., 2015) which lead to its anxiogenic effects (O'Brien et al., 2013); thereby suggesting that a ‘neutral antagonist’ may be a more viable treatment option. Various research groups are developing and testing CB1 antagonists, with the aim of creating a compound with little or no negative psychiatric effects.

While pharmaceutical companies are looking to develop a CB1 neutral antagonist, Cannabis, the ‘Treasure chest of Pharmaceutical Drugs’, already contains a ‘neutral antagonist’ of CB1, Δ9-tetrahydrocannabivarin (THCV)(McPartland et al., 2015) Medicinal Cannabis companies and dispensaries often sell specialised strains which are designed to increase or decrease appetite. Although most strains of Cannabis contain Δ9-tetrahydrocannabinol (THC) which is a CB1 receptor agonist, and therefore cause the ‘Munchies’, there are specific strains which are thought to reduce appetite due to the high presence of THCV. One such strain (“Doug’s Varin”) has an extremely high percentage of THCV, and is used as an appetite suppressant by users of medicinal cannabis.

While blocking the CB1 receptor can help treat obesity, activating the CB1 receptor can be used in the treatment of anorexia nervosa and anorexia cachexia. The naturally occurring CB1 agonist in Cannabis is THC and has already been shown to have significant effects on the treatment of anorexia nervosa (Andries et al., 2014) and anorexia cachexia (Strasser et al., 2006). Especially for cachexia induced by chemotherapy, medicinal cannabis treatment has
shown to be extremely beneficial in increasing the quality of life of patients in many anecdotal cases, and this maybe from direct action on the CB₁ receptor (Abrams and Guzman, 2015).

**Figure 2**: The CB₁ receptor plays a critical role in the stimulation and blocking of appetite via multiple neurological pathways

If the psychotropic effects of THC are unwanted, a weaker CB₁ agonist, Cannabinol (also derived from Cannabis) can be used to treat anorexia nervosa and anorexia cachexia without causing the ‘high’, as it is non-psychotropic (Izzo et al., 2009). A study showed that Cannabinol did not impair motor coordination (Farrimond et al., 2012). Repeated dosages of Cannabinol can be delivered with comparable appetite inducing effects of THC, but without the side effects of motor incoordination and cognitive impairment typically seen with THC.

It is important to note that chemotherapy patients suffering from cachexia attain incredible relief from medicinal cannabis, not only for its ability to cause the ‘Munchies’, but also due to the multifaceted therapeutic effects it can have. These effects may be to increase mood, alleviate pain and decrease nausea (often associated with chemotherapy).

**Future directions**

Due to the CB₁ receptor’s central role in the human appetite axis, and the presence of CB₁ receptor agonists and antagonists within the Cannabis plant; research on the plant’s derivatives is an obvious direction. Basic research on its components can lead to the recreation of their synergistic effect with the final aim of treating the appetite disorders more effectively.
References


