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A brief review on the use of cannabis as a treatment option for local inflammation in peripheral tissue

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Abstract
Inflammation is a complex process which, ideally, comes about as a "mop up' response to cell injury. It however occasionally results in undesired effects that should otherwise be prevented or resolved speedily. There are available numerous medicines with varied modes of administration commercially available for the management of inflammation. With the growing evidence of cannabis' therapeutic effects, its anti-inflammatory properties being one of them, debates among proponents and opponents of cannabis use are ever growing. These debates are centered on the undesired central effects of some of the plants secondary metabolites an argument that can be moderated by using the plant in a manner that steers clear of these effects. Effective topical formulations could very well be one avenue through which nature can be allowed to heal with minimal negative repercussions.

Keywords: Inflammation, cannabinoid receptors, cannabinoids, topical preparations

Introduction
Inflammation comes as a result of complex changes that occur in a tissue secondary to localized skin damage. Any injury to a cell or tissue is caused by a variety of phenomena such as oxygen deprivation, nutritional imbalances, infectious agents, immunological reactions, genetic defects, nutritional imbalances, physical agents and aging. Once injury to a cell or tissue occurs a cascade of dramatic changes in the surrounding tissue begin that are characterized by vasodilation, leaking of fluid from capillaries, clot formation in interstitial space, migration of leukocytes to injury site and subsequent swelling of tissues. This response has a protective role that is intended to ensure return to a homeostatic phase which is achieved by diluting, destroying and/or neutralizing harmful agents in other words 'mopping up" of the destroyed tissue. The intensity of the inflammatory processes is usually proportional to the degree of tissue injury (Guyton & Hall, 2006) [13]. Resolution of inflammation begins when the inflammatory stimuli are removed and the mediators are inhibited, catabolized or dissipated (Kumar, Cotran, & Robbins, 2003) [21]. However if the response is inappropriately deployed, the results may be deleterious as seen in some disease processes such as rheumatoid arthritis, atherosclerosis, asthma and the lethal anaphylaxis (Guyton & Hall, 2006) [13]. Hypersensitivity reactions, autoimmune diseases and chronic release of inflammatory mediators are examples of inflammation response resulting in disease process. Disease processes resulting from inflammatory response are undesirable more so that these events are intended to play a protective and survival role rather than be the cause of maladies.

The inflammatory process is initiated by the release of chemical mediators from cells, this is as a result of cell destruction or its interaction with innocuous substances. Examples of these mediators include; prostaglandins, histamine, serotonin, pro-inflammatory cytokines and inflammatory neuropeptides that are released from cells such as mast cells, macrophages and sensory neurons. The type and quantity of the mediators released varies according to the type and intensity of the injury. Once released this variety of tissue products of inflammation leads to a chain of reactions that ultimately, macroscopically, results in an area that is reddened, swollen, hot, and painful with alteration or loss of function. Thus, effects of inflammatory response, besides being a mode of survival, can be unpleasant especially when inappropriately deployed. (Rang, Dale, Ritter, & Moore, 2003). Prevention or speedy resolution of inflammation therefore, become a desired goal of therapy. This is achieved by release prevention, neutralization or inhibition of inflammatory mediators. The cellular events occurring in the inflammatory response are complex and beyond the scope of this paper, however the attention is drawn to the role that mast-cells, macrophages and sensory neurons play in the cascade and how cannabinoids affect them.

Inflammation and Cannabinoid Receptors

All mammalian cells, mast, macrophages and neurons included, possess protein targets through which chemicals interact with the cells to illicit a response. These targets are broadly categorized as receptors, ion channels, enzymes and carrier molecule (Rang, Dale, Ritter, & Moore, 2003) [27]. Receptors are protein molecules found in/on a cell to which messenger molecules/ligands bind and initiate physiologic changes within the cell. Of particular interest in this study are receptors present in the cells that play a role in inflammation. In 1990 a scientist named Matsuda cloned a receptor that was referred to as Cannabinoid Receptor (CBR), three years later a similar receptor was cloned and the two were subsequently named Cannabinoid receptor 1 (CB1) and Cannabinoid receptor 2 (CB2) respectively. The receptors are so named after phytochemicals called cannabinoids that act as ligands of the receptors and are unique to the cannabis plant (Hazekamp, 2007) [15]. Cannabinoid receptors are typically members of the G-protein coupled receptors (GPCR) linked to inhibition of adenylate cyclase. The CBRs are also linked to some ion channels and result in potassium activation and calcium inhibition which has an inhibitory effect on neurotransmitter release (Rang, Dale, Ritter & Moore).

CB1 are primarily found in the brain and sparsely in peripheral tissues and organs and have been determined to have an inhibitory role on cyclic AMP activity and N-type calcium channels which generally results in suppression of neuronal excitability and inhibition of neurotransmission. The peripheral tissues in which CB1 is expressed include immune tissues and sensory neurons among others. CB2 receptors on the other hand are periferous and are primarily expressed by immune tissues such as leukocytes, tonsils and spleen. The role of CB2 is yet to be clearly understood but researchers agree that they have some relevance in immune modulation in relation to cytokine release. (Pertwee, 1998; Barrer, Barman, Boitano & Heddwen, 2012; Hazekamp, 2007; Mackie 2008) [15, 22].

In inflammation modulation, the CB1 and CB2 have varied physiological responses following activation of the receptors by ligands. There exists a variety of such ligands that are categorized as endogenous, plant derived or otherwise synthetic (Hazekamp, 2007) [15]. As stated earlier, stimulation of CB1 receptors suppresses neuronal excitability and inhibits neurotransmission an effect that potentially aids in inflammation resolution or prevention. In an experimental model of the Male-Sprague rat's hind paw, Richardson and colleagues were able to demonstrate that activation of CB1 receptors on the peripheral afferent neurons possibly resulted in inhibition of neuropeptide release and concluded that this inhibition could result in anti-inflammatory and antihyperalgesic effects. It so happens that neuropeptide release results in amplification of the inflammation cascade thus inhibition of this action down-regulates the process ultimately resulting in anti-inflammatory effects (Richardson, Kilo, & Hargreaves, 1998) [28]. In an inflammatory response, neuropeptide release results in secretion of tachykinins (neurokinin A and substance P), calcitonin gene-related peptide. The secreted tachykinins and peptides acting in synergy with other inflammatory mediators potentiate vasodilation in surrounding tissues and nociceptor stimulation in the afferent C fibers. Thus inhibition of neuropeptide release as a result of CB1 stimulation maybe of therapeutic significance particularly in neurogenic inflammation (Barry, 2007) [1] (Rang, Dale, Ritter, & Moore, 2003) [27] Besides the role of CB2 receptors not being clearly understood, it is believed that stimulation of the CB2 receptors in Mast cells inhibit their degranulation a process that results in release of histamine and serotonin. The consequence of release of these mediators are vasodilation, leaking of plasma in interstitial space and activation of nociceptors these processes are observed macroscopically as reddening, swelling and pain. This release and subsequent consequences are however inhibited by CB2 stimulation (Richardson, Kilo, & Hargreaves, 1998) [28]. In a review article Kaminski made mention of an experimental model which observed stimulation of CB2 receptors. The results of that experiment showed that stimulation of the receptors expressed by macrophages resulted in inhibition of DNA binding the main nuclear transcription factors that are vital in regulation of cytokine and inflammatory mediator genes (Kaminski, 1998). Paradoxically, other experimental models showed an increase in inflammatory mediators such as Nitric Oxide and Interleukin-1 in T and B cells of the immune system. These differences could be attributed to varied experimental models though the writer states that cannabinoid receptor activation enhances humoral immunity while inhibiting the cell mediated immunity resulting in an overall decrease in immune response in peripheral tissues (Klein, Newton, & Friedman, 1998) [20].

It is clear that stimulation of cannabinoid receptors has immune modulatory effects that ultimately contribute to resolution of inflammation by inhibiting release of pro-inflammatory mediators, chemokines and neuropeptides that would otherwise escalate the inflammatory response by enhancing both the vascular and cellular events that occur in inflammatory cascade. This overall effect is observed in both CB1 and CB2 receptors even though the precise physiological changes occurring at the receptors are varied.

Cannabis in Therapeutics

The process of therapeutics begins with identification of the target site on which a drug molecule will attach and subsequent physiological changes that will result from the interaction. Discovery and cloning of the CB receptors was a consequence of researchers trying to understand how extracts of the cannabis plant affected the human body, particularly the psychoactive effects observed following administration. Cannabis had been used as a medicine for thousands of years dating back to 2700 BC as mentioned in a Chinese herbal. Accounts of its use are also present in Assyrian, Greek and Roman texts. In the 19th Century, a Chemist and Apothecarist named Michael Donovan published work on cannabis use in various ailments. He attests that it was highly effective in cases of violent neuralgic pain in the arms and fingers, inflammation of the knee, facial neuralgia and sciatica. Other physicians also wrote on its use in rheumatic pain and toothache. It goes without saying that identification of the receptors led to better understanding of the mechanism through which the plant extract elicited its therapeutic as well as undesired effects (Price & Notcutt, 1998) [26] (Hudson & Puvanenthirarajah, 2008) [16].

Chemical compounds that interact with the CB receptors, ligands, are referred to as cannabinoids. The initially known cannabinoids were those of plant origin, referred to as phytocannabinoids, whose identification was a result of work pioneered by Mechoulam and colleagues. The past two decades have seen discovery of cannabinoids that are synthesized in the body termed endocannabinoids and finally through pharmaceutical research synthetic cannabinoids have been developed. (Hazekamp, 2007) [15] (Barry, 2007) [1]

(Phillips, 1998) [25]. Phytocannabinoids are of particular interest and researchers seem to agree that their full therapeutic potential is yet to be realized.

Cannabis, an annual plant, is herbaceous and dioecious with varying height and branching depending on the environment and genetic factors. Monoecious plants do occur rarely. The plant is classified taxonomically as a mono species but shows considerable variation in cannabinoid content. The variations are in quantity and portion, depending on cultivar, cultivation conditions and methods of extraction (ElSohly, *et al*., 2013) [7] (Hazekamp, 2007) [15] (Brown D.T., 1998) [5]. There are currently over 7000 publications on cannabis and its constituents, the plant is known to contain more than 750 secondary metabolites including alkaloids, phenols, terpenoids and cannabinoids. Phytocannabinoids are 21-C compounds believed to be unique to the cannabis plant biosynthetically produced from Olivetolic acid and Geranyl diphosphate. Currently over 66 phytocannabinoids have been identified and among these 11 are characterized. Among the phytocannabinoids, delta-9- Tetrahydrocannabinol (Δ-9-THC) is relatively widely studied mostly due to its psychoactive effects. The other principle cannabinoids are cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG) and cannabichromene (CBC) and their carboxylic acids (ElSohly, *et al*., 2013) (Hazekamp, 2007) [15] (Evans, 2002) [8] (Zwenger, 2014) [31]

CB receptors are G-Protein Coupled Receptor hence principles relating to ligand-receptor interactions do apply, in relation to CB receptors, the concepts of partial agonism, functional selectivity and inverse agonism have been observed (Mackie, 2008) [22]. A conclusion can be drawn that although structurally similar, different cannabinoids will have varied physiological effects resulting from the interaction with receptors. Other studies have revealed that some cannabinoids that have low affinity for CB receptors either individually or collectively still exert some changes that are mediated by the receptors. One such cannabinoid is CBD, to explain this, scientists hypothesize that the cannabinoid promotes various homeostatic and immune modulating effects by binding to receptors other than the CB receptors (Talleyrand, 2017) [30]. The receptors implicated in this hypothesis include other G-protein coupled receptors, alpha-7 nicotinic receptors, 5-Hydroxytryptamine receptors, vanilloid receptors, peroxisome proliferation-activated receptors in addition to potassium channels, a phenomenon referred to as "off- target action" (Fowler, 2008) [11] (Mackie, 2008) [22] (Talleyrand, 2017) [30].

This off target effect could be the reason why some cannabis users claim that the plant extract is more useful than a single cannabinoid in management of some ailments (Hazekamp, 2007) [15] (Evans, 2002) [8]. A significant result of research has been production of single cannabinoids both plant sourced and synthesized that are available commercially for alleviating a variety of maladies in some cases inflammation and auto-immunity are part of the disease process. Further studies also suggest that compounds present in the cannabis plant that are structurally and biologically distinct from cannabinoids have significant inhibitory effect on prostaglandin release however, use of cannabis as an anti-inflammatory drug is inconclusive (Brown D.T., 1998) [6]. Price and Notcutt have recommended that the way forward in advancing cannabis use for pain relief (including pain resulting from inflammation) requires identification and isolation of all the active components and conducting properly planned clinical trials with a suitable route of delivery (Price & Notcutt, 1998) [26]. The most common routes of cannabis administration are inhalation and ingestion (Talleyrand, 2017) [30], these modes do however result in systemic effects something that is best avoided in a situation where the drug target is localized peripheral tissue.

Topical Preparations

Topical preparations are applied to the skin mainly for local action. The skin comprises the epidermis, dermis and subcutaneous tissue as well as a number of appendages. Skin penetration of drugs depends on physicochemical properties of the drug and the state and area of the skin. Other important considerations to make when an effectiveness topical agent is desired are that the drug should elicit a pharmacological effect, the skin should be penetrable and the vehicle should release the medicament at the ideal rate (Barry, 2007) [1].

Topical agents for pain relief in peripheral and local conditions are not routinely used due to relatively low availability. There is however increasing evidence supporting the efficacy of these preparations in nociceptive and neuropathic pain. An added advantage of topical formulations are good safety profile and ease of administration particularly in pediatrics and geriatrics. There are some studies that have demonstrated analgesic effects of some cannabinoids in animal models of inflammatory and neuropathic pain. It is also known that Δ8 THC, CBN and CBD extracted from Cannabis sativa L. act at peripheral sites and yield analgesia through CB1 and CB2 receptor mediated action. This subject however still requires further clinical trials as agreed by most scientists (Jorge, Feres, & Teles, 2011) [18]. Pain and inflammation are hardly synonymous in scientific research however there is a significant relationship in view of symptoms. Inflammation will usually result in a subject experiencing pain due to sensitization of nociceptors by various inflammatory processes. Pain however is a complex subjective phenomenon that is challenging to define (Odendal, 2010) [23].

Cannabinoids have a low-water solubility, a property that have been viewed as hindrance in development of effective formulations for human use. The lipophilic property however allows cannabinoids to penetrate cellular membranes by diffusion (Hazekamp, 2007) [15] making it a potential candidate for topical administration. Referring to the checklist for effective topical agents: it is known that cells expressing CB receptors are present in peripheral tissue thus, a pharmacological effect will be elicited following interaction with a ligand; the cannabinoids easily diffuse through the skin owing to the lipophilic nature; and some solvents used in their extraction can be incorporated in the formulation.

The cannabis resin is soluble in alcohol, ether, carbon disulphide, n-Hexane and chloroform (Evans, 2002) [8] (Hazekamp, 2007) [15]. Oils and butters are also used for extraction and formulation (San Francisco USA Patent No. US 8, 425,9 54, B2, 2013). A study comparing cannabinoid solubility in organic solvents revealed that chloroform was the most efficient solvent compared to light petroleum each solvent recording a 98-100% and 94-99% extraction of cannabinoids respectively. Ethanol was also used but proved unsuitable for the experimental design due to its ability to extract ballast substances as well (Fairnarin & Liebmann, 1973) [9].

Topical formulations can be prepared readily following cannabinoid extraction using the solvents mentioned. Chloroform besides being the most efficient solvent would readily evaporate out of solution implying that the final

product would be devoid of the extracting solvent (Billany, 2007) [2]. This however is preferred given the reported hepatotoxic and mutagenic effects of chloroform (Bonauto, Brodkin, & Robertson, 2001) [4]. Formulations containing alcohol have a cooling effect once the alcohol evaporates from the skin, a property that would be appreciated in a case where inflammation is characterized by hotness. Alcohol also has an added advantage of having antimicrobial effects this could potentially contribute to elongation of the product shelf life (Hanlon & Hodges, 2007) [14]. Oils and butters are also well suited as vehicles in topical preparations because they form a protective layer thereby hydrating the skin and further enhancing penetration of the medicament through the stratum corneum. Alternatively they can be formulated as emulsions that are relatively considered more pleasant than oily applications (Billany, 2007) [2].

Conclusion

For any topical preparation to be effective it should be able to reach the site of action and elicit a pharmacological response. There are a number of considerations to be made in this regard these include physical-chemical properties of the drug and stability of the formulation among others. Topical cannabis has potential as a therapeutic option for local inflammation in peripheral tissue however, more research needs to be conducted to establish the most suited formulation, standardize the cannabinoid content that will be effective as well as determine disease states in which these formulations will be applicable. A 'fix all' formulation does not exist however, the search for alternative and/or better treatment options is what the pharmaceutical community is constantly striving for.

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