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REVIEW AND BIOINFORMATICS RESEARCH

Expression of the endocannabinoid system in fibroblasts and myofascial tissues

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Summary The endocannabinoid (eCB) system, like the better-known endorphin system, consists of cell membrane receptors, endogenous ligands and ligand-metabolizing enzymes. Two cannabinoid receptors are known: CB_1 is principally located in the nervous system, whereas CB_2 is primarily associated with the immune system. Two eCB ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are mimicked by cannabis plant compounds. The first purpose of this paper was to review the eCB system in detail, highlighting aspects of interest to bodyworkers, especially eCB modulation of pain and inflammation. Evidence suggests the eCB system may help resolve myofascial trigger points and relieve symptoms of fibromyalgia. However, expression of the eCB system in myofascial tissues has not been established. The second purpose of this paper was to investigate the eCB system in fibroblasts and other fascia-related cells. The investigation used a bioinformatics approach, obtaining microarray data via the GEO database (www.ncbi.nlm.nih.gov/geo/). GEO data mining revealed that fibroblasts, myofibroblasts, chondrocytes and synoviocytes expressed CB_1, CB_2 and eCB ligand-metabolizing enzymes. Fibroblast CB_1 levels nearly equalled levels expressed by adipocytes. CB_1 levels upregulated after exposure to inflammatory cytokines and equiaxial stretching of fibroblasts. The eCB system affects fibroblast remodeling through lipid rafts associated with focal adhesions and dampens cartilage destruction by decreasing fibroblast-secreted metalloproteinase enzymes. In conclusion, the eCB system helps shape biodynamic embryological development, diminishes nociception and pain, reduces inflammation in myofascial tissues and plays a role in fascial reorganization. Practitioners wield several tools that upregulate eCB activity, including myofascial manipulation, diet and lifestyle modifications, and pharmaceutical approaches.

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Introduction

The introduction comprises a broad review of the endogenous cannabinoid (eCB) system, in three sections: 1. cannabinoid receptors, 2. eCB ligands, 3. clinical aspects of receptors and ligands. Ligands that bind to receptors may activate receptors (''agonists'') or deactivate receptors (''inverse agonists''). The chemical concepts underlying eCB research may raise anxiety in clinicians. However, the realization that *chemistry is structure* (Ingber, 1998) makes many of these concepts readily understood by bodyworkers. For example, the pharmacological principle of structure–activity relationships (SARs) is analogous to the anatomical concept of structure–function relationships.

After the introduction, this paper investigates the eCB system in fibroblasts, utilizing a bioinformatics approach. Bioinformatics uses networks of computers, software algorithms and internet-accessible databanks to organize, analyze, and predict biological structure and function. This approach poses a new challenge to clinicians, impelling them to grasp the utility and ease of ''GEO,'' the bioinformatics tool used in this study. Bioinformatics democratizes the research process; all one needs is computer access and imaginative questions. Several pre-publication reviewers of this paper immediately grasped GEO to answer questions of their own. The paper finishes with a discussion of clinical applications. The discussion delivers a unique perspective not heretofore presented in the literature—that our task as clinicians who treat pain and myofascial dysfunction is to enhance endogenous eCB activity in our patients.

Cannabinoid receptors

Cannabinoid receptors (CBRs) take their name from the *Cannabis* plant. The *Cannabis* plant is a source of *exogenous* ligands. The ligands are lipophilic (i.e., water-insoluble), thus difficult to study, and took 150 yr to elucidate. Finally, in 1964, Raphael Mechoulam isolated Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Since then, Raphael Mechoulam, Roger Pertwee and many others have identified more than 70 unique *Cannabis* compounds, collectively called the cannabinoids (reviewed in Pertwee, 2005). Candice Pert's co-discovery of the μ-opioid receptor in 1973 launched a quest for CBRs. But CBR discovery awaited the development of water-soluble synthetic THC analogs, such as CP55, 940. In 1988 Allyn Howlett and Bill Devane showed that [^{3}H]CP55, 940 bound to a receptor located in the cell membrane of the neuronal (brain) cells. Two years later, Lisa Matsuda cloned the gene for the CBR and decoded its DNA sequence. The cDNA sequence translates into a chain of 472 amino acids that weave back and forth across the cell membrane. This topology is characteristic of a G-protein-coupled receptor (GPCR). GPCRs are named after their G-proteins, short for guanine nucleotide binding proteins, which function as intracellular ''molecular switches.'' GPCRs include opioid receptors, dopamine receptors, serotonin receptors and many others (reviewed in Howlett et al., 2002).

A second CBR was discovered in 1993, so the receptors became known as CB_1 and CB_2. The two receptors express slightly different structures and slightly different functions: CB_1 principally functions in the nervous system, whereas CB_2 is primarily associated with cells governing immune function, such as white blood cells. Taken together, CB_1 and CB_2 bridge the constituent parts of psychoneuroimmunology and represent a microcosm of mind-body medicine. CB_1 and CB_2 are tensegrity structures that span the cell membrane. A ligand that loads the receptor's *extracellular* surface will distort the shape of its *transmembrane* weave of amino acids, thereby altering the *intracellular* side of the receptor and its interface with the G-protein. This shape-altering ''conformational change'' in the receptor activates the G-protein, which disconnects from the receptor, splits into subunits, and the subunits move around the inside of the cell. The activated G-protein subunits further transduce signal by reorganizing other tensegrity structures (e.g., enzymes and ion channels), causing a ''cascade'' that ultimately governs gene expression and cell behavior. Steve Ingber characterized tensegrity structures as the hardware behind living systems, and signal transduction machinery as the software (Ingber, 1998).

CB_1 is the most common GPCR neuroreceptor in the human brain, but it is distributed unevenly. Highest densities of CB_1 are found in the hippocampus (affecting short-term memory) and parts of the basal ganglia (e.g., the substantia nigra, globus pallidus and the striatum (caudate and putamen)). CB_1 in these nuclei coordinate movement, as does CB_1 in the cerebellum. High densities in the cerebral cortex, amygdala and dorsal horn of the spinal cord affect cognition, mood and emotion, and pain perception. Very low densities are found in the brainstem cardiorespiratory centers, which probably accounts for the lack of lethal effects from cannabis overdose (reviewed in Howlett et al., 2002).