Editorial

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Cannabinoids in Health and Disease

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Itai Bab, In Memoriam

Prof. Itai Bab was born in Rehovot, Israel, in 1945. His father escaped the Nazis and emigrated from Germany to Israel in the mid-1930s. His mother was fifth-generation Israeli with Russian ancestors. He finished his studies as a Doctor of Dental Medicine at the Hadassah School of Dental Medicine, Hebrew University of Jerusalem, Israel. In 1976, he joined the Oral Pathology Department in that school. In parallel to his clinical work and teaching, Itai joined the research laboratory of Prof. Jona Sela and has contributed greatly to the understanding of biological mineralization. After working for 2 years at Prof. M. Owen’s laboratory in Oxford, he established his own laboratory in Jerusalem, where he developed tissue culture techniques. In cultures of bone marrow stromal cells such as osteoblasts, derived from human and other mammalian species, Itai identified osteogenic growth peptide (OGP) as a regulator of proliferation as well as alkaline phosphatase activity and matrix mineralization via an autocrine/paracrine mechanism. He showed that OGP also regulates the expression of type I collagen and the receptor for basic fibroblast growth factor in vivo. These innovative findings attracted considerable clinical interest.

In the early 2000s, Itai was drawn to the nascent research field of endocannabinoids (eCB). As a pioneer in this field, he revealed novel aspects of eCB signaling in bone biology. Among his findings, Itai discovered skeletal CB receptors and the role of their endogenous ligands in bone mass regulation. As an interdisciplinary scientist, he collaborated with colleagues studying eCB signaling from various fields such as skeletal medicine, neuroendocrinology, cannabinoid research, and neuropsychiatry.

Itai’s publications, including 135 peer-reviewed manuscripts, in journals such as FASEB J, Blood, EMBO, JBMR, Gastroenterology, and PNAS reflects his major scientific contributions. Of special note is Bab et al., Micro-tomographic atlas of the mouse skeleton, published in 2007, which is considered a primary reference for researchers in bone biology and related fields.

Itai has supervised numerous students at various levels, and the following words, written by one of them, attest to his dedication and special relationship with his mentees:

“As his PhD student, he was always there for me; coaching, mentoring, encouraging, and sometimes pushing hard for me to keep on fighting the good fights. Later, at my post-doc training at the NIH, he continued to mentor me and was never tired of listening to me tell him all about my research adventures. Now, as a new Assistant Professor I teach, coach and mentor everal students. Indeed, with Itai’s vigorous training, and by allowing me to build my own confidence as a researcher, I owe him what I am today. He indeed had a pivotal influence on my life and career. I salute you, Itai!”

Besides being a great scientist, Itai was a loving and devoted family man to his wife and three children and a most proud and happy grandfather. His unexpected passing is a great loss to them and to his many friends and colleagues at home and abroad.

This issue of the Journal of Biological and Clinical Physiology and Pharmacology (JBCPP) is dedicated to Itai’s memory and includes manuscripts submitted by his colleagues and discusses various aspects of the eCB system in Health and Disease.
Editorial: Cannabinoids in Health and Disease

In the three decades following the isolation of the psychoactive ingredient of *Cannabis sativa*, Δ(9)-tetrahydrocannabinol (THC) by Gaoni and Mechoulam in 1964 [1], the endogenous counterparts of THC, collectively termed endocannabinoids (eCBs), were discovered along with their receptors and synthetic-metabolic machinery. The eCBs are now recognized as key mediators in both human physiology and pathology. The present issue of the *JBCPP* describes many aspects of these versatile molecules including clinical applications and novel therapeutic targets. The first article by Mechoulam [2] presents the historical uses of cannabis in the Middle East and the more recent scientific and medical research on phytocannabinoids and the eCB system, with emphasis on the Israeli perspective – research contributions from Israel.

**Analgesic effects**

The most common clinical indication for cannabinoid use is reviewed by Lynch in “Cannabinoids in the management of chronic pain: a front line clinical perspective” [3]. Chronic pain is a major public health concern, and available treatments are inadequate. Preclinical research has identified a sophisticated endocannabinoid system within the natural pain and immune defense networks. Recent systematic reviews concluded that cannabinoids currently available for clinical use are safe for the management of chronic pain.

**CNS-related effects**

**Anxiety**

The endocannabinoid system is important in emotional control, and its dysregulation has been implicated in several psychiatric disorders. The most common self-reported reason for using cannabis is to reduce feelings of stress, tension, and anxiety. The review by Akirav and co-workers in “Targeting the endocannabinoid system to treat anxiety-related disorders” [4] describes the evidence that the endocannabinoid system is useful in preventing and treating anxiety-like behavior in animal models and post-traumatic stress disorder (PTSD) patients. The author suggests that this system is a novel and attractive therapeutic target for treating anxiety-related disorders in general and PTSD in particular.

**Depression**

Certain animal behaviors are modulated by selective disruptions of bone formation. Furthermore, the brain regulates bone remodeling through sympathetic and parasympathetic nerve fibers. Importantly, norepinephrine release from sympathetic terminals in the bone is inhibited by cannabinoid CB1 receptor activation by eCBs produced by osteoblasts. The study by Zimmer et al., “Behavioral changes induced by a conditional disruption of bone formation” [5], demonstrates that mice with reduced bone mass are more prone to depression-related phenotypes.

**Neuroprotection**

The role of 2-arachidonoyl glycerol (2-AG) and arachidonoyl-serine (AraS) as brain-derived “endogenous neuroprotective” agents has been described in a closed head injury model. In recent years, a library of approximately 70 N-acyl amino acids (NAAAs) structurally related to eCBs was discovered in the rat brain. The report by Mann et al. [6] addressed the question “are the endocannabinoid-like compounds N-acyl aminoacids (NAAA) neuroprotective after traumatic brain injury?” They examined members of the NAAA family with structural similarity to AraS, namely, palmitoyl serine (PalmS) and oleoyl serine (OleoS). The latter did not improve recovery after injury, whereas the former provided some neuroprotection, but less than 2-AG and AraS, via as yet unknown mechanisms.

**Tolerance and dependence**

Repeated treatment with THC produces common CB1 receptor-dependent pharmacological effects (i.e. catalepsy, hypothermia, antinociception, and hypolocomotion). The report by Lichtman and co-workers, “Pharmacological characterization of repeated administration of the first generation abused synthetic cannabinoid CP47,497” [7], describes the pharmacological cannabinimetic effects of CP47,497. Their findings indicate tolerance.
and dependence following repeated administration and show cross-tolerance following repeated THC administration, further suggesting a common cannabimimetic mechanism of action.

**Skeletal system**

**Signaling in brain and bone**

The short review entitled “A collaboration investigating endocannabinoid signaling in brain and bone” [8] is Zimmer’s account of his interdisciplinary collaboration with Itai Bab. He describes the discovery of the endocannabinoid system in bone and the analysis of its functions. The modulatory impact of CB1 in sympathetic inhibition of bone formation and the role of CB2 on osteoblast and osteoclast proliferation and functions are summarized. The clinical relevance of these signaling mechanisms is shown by the association of polymorphism in the CB2 receptor gene, CNR2, with bone density and osteoporosis. The review also summarizes the role of endocannabinoid signaling in bone elongation.

In the review article “The skeletal endocannabinoid system: clinical and experimental insights” [9], Raphael and Gabet focused on the roles of the endocannabinoid system in skeletal biology including the cannabinoid receptors. Controversies in the literature and potential therapeutic approaches targeting the endocannabinoid system in skeletal disorders are also discussed.

**Levels of bioactive lipids in cooking oils**

Rates of osteoporosis are significantly lower in regions of the world where olive oil is a dietary cornerstone. Olive oil is a source of oleoyl serine (OS), with known efficacy in animal models of osteoporosis. Bradshaw and Leishman screened several cooking oils and described their findings in the article “Levels of bioactive lipids in cooking oils: olive oil is the richest source of oleoyl serine” [10]. They noted that cooking oils contain varying levels of bioactive lipids from the endocannabinoid-like family of N-acyl amide and 2-acyl glycerol. Olive oil has the second highest number of lipids detected (20/33). Olive oil is a dietary source of OS, which may contribute to lowered prevalence of osteoporosis in countries with high consumption of this oil.

**Peripheral diseases**

**Ocular diseases**

Since the 1970s, when the observation that marijuana reduces intraocular pressure was made, its use as a therapeutic agent has been investigated. The review by Cairns et al. in “Seeing over the horizon – targeting the endocannabinoid system for the treatment of ocular disease” [11] summarizes the use of eCS-modulating drugs for the treatment of glaucoma and other ocular inflammatory and ischemic diseases.

**Kidney diseases**

“The emerging role of the endocannabinoid system in the pathogenesis and treatment of kidney diseases” is the title of Tam’s review [12]. The roles of the eCB system in normal kidney function and in diseases such as diabetes and obesity that directly contribute to renal pathologies are described. Activation of the CB1 receptor regulates renal vascular hemodynamics, yet in mouse and rat models of obesity and type 1 and 2 diabetes mellitus, eCBs contributed to the development of oxidative stress, inflammation, and renal fibrosis. These effects can be ameliorated by CB1 receptor blockers. Considering that the therapeutic potential of globally acting CB1 receptor antagonists is limited due to the adverse neuropsychiatric effects, peripherally restricted CB1 receptor antagonists may represent a novel pharmacological approach in treating renal diseases.

**Spermatotoxic effects**

The mechanisms by which *C. sativa* exerts spermatotoxic effects may include oxidative stress. Therefore, Alagbonsi et al., in his article “Melatonin and vitamin C exacerbate Cannabis sativa-induced testicular damage when administered separately but ameliorate it when combined in rats” [13], examined the effect of the antioxidants melatonin and vitamin C on *C. sativa*-induced spermatotoxicity. In their manuscript, they showed that these antioxidants exacerbate *C. sativa*-induced testicular damage in rats when administered separately but ameliorate it when combined.
Mechanisms of action

Neuro-inflammation

Synthetic derivatives of phytocannabinoids are used to study the mechanism(s) of action of this family of lipid mediators. Dimethylheptyl-cannabidiol (DMH-CBD) is one such derivative that is non-psychoactive and has anti-inflammatory properties. The effects of DMH-CBD at the transcriptional level are reported by Juknat et al. in their paper “Anti-inflammatory effects of the cannabidiol derivative dimethylheptyl-cannabidiol – studies in BV-2 microglia and encephalitogenic T cells” [14]. They found that DMH-CBD, in a manner similar to CBD, down-regulates the expression of inflammatory cytokines and protects the microglial cells and, as such, could be of high therapeutic value in neuro-inflammatory diseases and related syndromes.

GPR55 receptors (1)

Despite low homology with CB1 and CB2 receptors, GPR55 shares numerous cannabinoid ligands with them. The pharmacology of GPR55 had not been fully elucidated; however, in the review “GPR55 – a putative “type 3” cannabinoid receptor in inflammation” by Yang et al. [15], the authors described how GPR55 has emerged as a receptor. Furthermore, the recent evidence of GPR55-CB1 and GPR55-CB2 heterodimerization and its ubiquitous distribution suggests that GPR55 is involved in many cellular and pathological processes and is a potential anti-inflammatory therapeutic target.

GPR55 receptors (2)

In their study “Modulation of a L-α-lysophosphatidylglycerol/GPR55 MAP kinase signalling by CB2 receptor agonists: identifying novel GPR55 inhibitors” [16], Anavi-Gofer et al. investigated the structure-activity relationship of CB2 receptor-selective agonists. They have identified ligands that act both as CB2 receptor agonists and GPR55 modulators yet lack direct GPR55 activity.

CB1 receptor signaling

The signaling of CB1 receptor was shown to stimulate Gi/o-dependent pathway. The study by Eldeep et al., “CB1 cannabinoid receptor-mediated increases in cyclic AMP accumulation are correlated with reduced Gi/o function” [17], addressed the question of whether the CB1R could couple with Gs. They have pharmacologically manipulated reverse Gi/o family activation and concluded that an attenuated inhibitory influence of Goi on adenylyl cyclase rather than Gs activation is responsible for the observed increased production of cAMP.

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