Chapter 1
Endocannabinoids and Monoamines: Modulating the Modulators

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Abstract The past decade has seen a tremendous growth in knowledge related to cannabinoid receptor signaling in brain. In addition, the impact and consequences of cannabinoid modulation of monoaminergic circuits are steadily emerging demonstrating a significant interaction between these two systems in a variety of psychiatric (affective disorders) and neurological disorders (neurodegeneration, pain). Areas to be covered in the accompanying chapters include an overview of the endocannabinoid system, a summary of current cannabinoid receptor nomenclature, and pharmacological principles as well as electrophysiological, biochemical, and behavioral evidence for cannabinoid modulation of dopaminergic, noradrenergic, and serotonergic circuitry.

As the most commonly used illicit drug, cannabis poses a serious risk for psychopathology (Ferdinand et al. 2005). Frequent use doubles the risk for depression and anxiety, and significantly decreases multiple indices of psychosocial functioning (Lundqvist 1995a, b, 2005, 2010; Lundqvist et al. 2001; Patton et al. 2002; Anglin et al. 2012). Although exposure to delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, is associated with a number of adverse psychological effects, recent evidence suggests that administration of synthetic cannabinoid receptor agonists/antagonists may hold some therapeutic potential. Furthermore, altering endogenous cannabinoid signaling by manipulating the metabolism and uptake of endogenous cannabinoids may provide clinical benefits. Therefore, elucidating neural targets of cannabinoids has significant public health relevance.

The past 2 decades have seen a tremendous growth in knowledge related to cannabinoid modulation of monoaminergic circuits and their interactions in a variety of psychiatric and neurological disorders. Despite increasing evidence from preclinical data suggesting that therapeutic use of cannabinoid-based drugs may outweigh any potential risks in certain serious medical conditions, the debate surrounding its

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widespread utility continues as regulatory concerns preclude a smooth transition of promising preclinical studies into clinical trial testing. This may persist in the near future as state and federal governments debate over regulation of medicinal applications of cannabis. Applications for medicinal cannabinoids that are already under investigation include the treatment of nausea, anorexia, neurodegeneration, inflammation, excitotoxicity, and pain. The appetitive and antiemetic properties of cannabinoids have led to the approval of their use in chemotherapy and AIDS patients. There is growing evidence for therapeutic cannabinoid effects on inflammatory and excitotoxic cellular processes that are linked to epilepsy, Parkinson's disease, amyotrophic lateral sclerosis, spasticity, and central nervous system (CNS) injury. The chapters, herein, review and discuss current insights into the brain endocannabinoid system, cannabinoid receptor signaling on synaptic plasticity, and potential therapeutic applications with a particular focus on endocannabinoid modulation of dopaminergic, noradrenergic, and serotonergic circuitry.

In the CNS, the endocannabinoid system (ECS) is involved in a variety of physiological functions because of abundant expression of its receptors and ligands (Herkenham et al. 1991; Mackie 2008). Endocannabinoids, anandamide (arachidonoyl ethanolamide) and 2-arachidonoylglycerol (2-AG), are arachidonic acid derivatives that exist as precursor lipids in the plasma membrane and are synthesized by the action of specific lipases under certain physiological or pathological conditions (Piomelli et al. 1998; Piomelli 2003, 2005; Basavarajappa 2007). Anandamide and 2-AG have been implicated in the control of emotional reactivity, motivated behaviors, and energy homeostasis primarily by actions on brain cannabinoid (CB) type 1 receptors (CB1r) (Martin 1986; Mechoulam, Parker et al. 2002). As one of the most abundant G protein coupled receptors (GPCRs) in the mammalian brain, CB1 receptors have been implicated in the regulation of learning and memory, food intake, pain, and mood. A second cannabinoid receptor, CB2r, expressed primarily in cells of the immune and hematopoietic systems has been reported in brain. Using a radiolabeled cannabinoid receptor agonist, Herkenham et al. (1991) mapped cannabinoid receptor binding sites throughout the rat brain. Within the brainstem, cannabinoid receptors are sparsely expressed in comparison to regions highly enriched in cannabinoid receptors such as the hippocampus, basal ganglia, cortex, and cerebellum. However, regions with low to moderate cannabinoid receptor binding were noted in noradrenergic brainstem nuclei such as the locus coeruleus (LC) and nucleus of the solitary tract (Herkenham et al. 1991). Interestingly, there have been reports of a lack of correlation between the density of CB1 receptors and the efficiency of receptor coupling (Breivogel et al. 1997).This may explain, in part, why functionally important responses can be manifested in areas with sparse CB1r labeling such as the brainstem and hypothalamus (Jamshidi and Taylor 2001; Rademacher et al. 2003). Mechanisms including receptor dimerization (Mackie 2005) or changes in signal amplification have been suggested. Along these lines, amplification of CB1 signaling has been reported by involvement of a protein kinase A-dependent phosphorylation of DARPP-32, achieved via modulation of dopamine D2 and adenosine A2A transmission (Andersson et al. 2005).

In Chap. 2, Kenneth Mackie describes the components of the endocannabinoid signaling system as well as an important functional role for endocannabinoids—their role in modulating diverse forms of synaptic plasticity. The notion that endocannabinoids can inhibit synaptic transmission, coupled with the observation that endocannabinoids are often produced under conditions of intense neuronal activity, underscores the importance of cannabinoid-induced modulation of synaptic transmission in a surprisingly diverse number of ways.

In Chap. 3, a summary of basic pharmacological definitions, principles, and mechanisms underlying cannabinoid receptor activation and current receptor nomenclature for classifying a target as a cannabinoid receptor is provided by Marcu et al. The authors consider and discuss a large number of emerging reports indicating that the resulting effects of endo-, phyto-, and synthetic cannabinoid interactions cannot be definitively explained based on a two-cannabinoid receptor theory. Therefore, the authors review the actions of endocannabinoids not restricted to the CB1r and CB2r, including additional GPCRs, ion channels, ion channel receptors (i.e., transient receptor potential cation channel; TRP) and nuclear receptors (peroxisome proliferator-activated receptor).

While amino acid transmitter systems (Kano et al. 2009) represent an important target of the ECS and exogenous cannabinoid-based drugs, interactions with monoaminergic circuitry has revealed important consequences for global effects on behavior. Accumulating evidence indicates a significant role of the cannabinoid system in the regulation of basal ganglia function, particularly with respect to reward, psychomotor function, and motor control. Dysfunction in the ECS is likely to impact dopamine- and basal ganglia related neurospsychiatric disorders, including drug addiction, psychosis, Parkinson's disease and Huntington's disease. The distribution of components of the ECS within basal ganglia networks suggest that the motivational and motor effects of cannabinoid-based ligands are modulated, in part, by dopamine transmission. In Chap. 4, De Witt et al. summarize a role for direct and indirect mechanisms underlying cannabinoid modulation of dopaminergic transmission. Specifically, the authors review existing evidence of cannabinoid modulation of excitatory and inhibitory networks in the reward system with the net effect of regulating the overall doapminergic 'reward tone'. Then, they discuss emerging evidence that cannabis exerts its addictive properties through effects of the ECS on the brain reward neurocircuitry. Specifically, the authors describe evidence for cue-elicited craving for marijuana, and, importantly, how in the absence of cannabis itself, cannabis-associated cues trigger activation in the reward pathway implicated in the neuropathology of addiction.

The use of synthetic cannabinoid receptor agonists/antagonists or compounds targeting endocannabinoid synthesis/metabolism in brain has received widespread attention as these approaches may hold some therapeutic potential for neurological and psychiatric disorders and has stimulated investigations into manipulating endogenous cannabinoids for potential clinical benefit. In Chap. 5, Matricon and Giuffrida discuss interactions between cannabinoids, dopamine and glutamate in the basal ganglia and review how targeting the cannabinoid receptor system might constitute an integrated pharmacotherapeutic approach in addressing the pathophysiology of

disorders characterized by dopamine dysfunction, such as Parkinson's disease and schizophrenia. Specifically, the authors summarize evidence supporting direct and indirect cannabinoid receptor agonists as promising antiparkinsonian, antidyskinetic, and antipsychotic-like properties in animal models but highlight the lack of large-scale clinical studies to translate these preclinical findings into new therapies.

As the ECS plays a role in the regulation of mood, accumulating evidence supports changes in the ECS by chronic treatment with antidepressants, including serotonin and/or norepinephrine reuptake inhibitors as well as monoamine oxidase inhibitors. In Chap. 6, Fisar reviews preclinical and clinical data supporting a critical role for monoamine neurotransmission in the neurochemistry of mood disorders. He discusses the pathophysiology of mood disorders from a perspective of dysfunction in energy metabolism of neurons, modulation of inflammatory pathways, changes in activities of transcription factors, neurotrophic factors and other components involved in neuroplasticity and apoptosis. The chapter continues from a perspective of neuromodulation of synapses by cannabinoids summarizing evidence showing that cannabinoids have the capacity to produce increased hippocampal neurogenesis and that this is positively correlated with its antidepressant effects.

The ability of cannabinoid agonists to enhance norepinephrine release plays a critical role in the mood altering properties and cognitive effects of cannabis-based compounds. One of the most significant behavioral signs associated with cannabinoid administration relates to impairment in attention, vigilance, and cognitive processing (Casswell and Marks 1973; Chait 1992). Long-term cannabis use results in impairment of attention that worsens with increasing years of regular use (Solowij et al. 2002). Studies examining the effects of cannabinoids on attention (Hillyard and Kutas 1983; Naatanen 1990) have shown that chronic cannabis use affects information processing (Kempel et al. 2003) where users are unable to effectively focus (Solowij et al. 1995). One neurochemical target at which cannabinoids may interact to have global effects on behavior is brain noradrenergic circuitry. Moreover, the noradrenergic system continues to be an important target in the development of new therapies for affective disorders because of its critical role in the modulation of emotional state and regulation of arousal and stress responses (Heninger and Charney 1988; Charney et al. 1989; Ballenger 2000; Carrasco and Van de Kar 2003). In Chap. 7, Carvalho and Van Bockstaele discuss anatomical, biochemical, and behavioral evidence for cannabinoid modulation of noradrenergic circuits and review the role of norepinephrine in cannabinoid-induced behaviors, specifically aversion. The authors summarize studies showing that brain noradrenergic transmitter and receptors are significantly impacted by cannabinoids. They review how, under basal conditions, exposure to a synthetic CB1r agonist increases anxiety-like behaviors that correlate with increases in multiple indices of brain noradrenergic activity. Interestingly, a different consequence to the regulation of norepinephrine by cannabinoids is observed under conditions of stress. Specifically, stress-induced increases in cortical NE levels are significantly attenuated by prior treatment with a CB1r agonist suggesting complex actions of cannabinoids on noradrenergic circuitry that vary under basal vs stress conditions. These findings indicate that, with respect to monoamine release, CB1r modulation is complex and can involve either stimula-

tion or inhibition of neurotransmitter released depending on neuronal state (Mackie 2005; Kano et al. 2009). This is consistent with studies showing that modulation of neurotransmitter release by cannabinoid receptor agonists can be different depending on neuronal firing rate (Roloff and Thayer 2009) and is likely to be dynamically regulated by stress. In Chap. 8, Gorzalka and Dang discuss evidence supporting the hypothalamic-pituitary-adrenal (HPA) axis as a major area of interaction between the endocannabinoid and the noradrenergic systems in mediating stress responses. By defining and paralleling the endocannabinoid and noradrenergic systems as 'gatekeepers', the authors discuss the role of norepinephrine in mediating physiological responses to stress by mobilizing the HPA axis and the ECS as preventing maladaptive HPA hyperactivation during chronic stress. Furthermore, the authors expand on the sexual dimorphism in both systems, and implications for psychiatric disorders, specifically depression.

Considerable evidence has accumulated to support the hypothesis that the ECS is altered by stress exposure and modulates stress responses through effects on synaptic activity. These data have important implications for therapeutic treatment of disorders in which hyperactive HPA axis activity contributes to disease. The CB1r is present in stress responsive circuits (frontal cortex, amygdala, and hypothalamus) that are essential to the expression of anxiety (Herkenham et al. 1990; Roloff and Thayer 2009; Oropeza 2005 #11). Acute restraint stress has been shown to increase the synthesis of endogenous endocannabinoids in limbic forebrain areas (Patel et al. 2005). In addition, release of endocannabinoids has been shown to mediate opioid-independent stress-induced analgesia by actions in the periaqueductal gray. Complex interactions exist between the cannabinoid system and stress responsivity. Low doses of cannabinoid agonists administered in familiar, nonstressful environments, typically result in positive responses such as enhanced euphoria and a reduction in anxiety (Hollister 1986). However, dysphoric reactions are commonly manifested as panic, anxiety, and paranoia and occur in response to high doses of consumption or when the drug is administered in environments that are stressful (Greggand Campbell 1976; Gregg et al. 1976). In Chap. 9, Hillard reviews how glucocorticoids mobilize endocannabinoids and how endocannabinoid-CB1r signaling serves as a primary regulator of synaptic plasticity via changes in presynaptic release, specifically subserving short-term, activity-driven changes in synaptic strength as well as other forms of presynaptic plasticity. She further discusses preclinical models that have suggested that therapeutic agents such as fatty acid amide hydroylxase (FAAH) inhibitors should be examined in humans for treatment of anxiety and depressive disorders that are characterized by excessive or prolonged HPA axis activation. This is based on studies showing that FAAH inhibition inhibits stress-induced increases in circulating glucocorticoids, reduces anxiety in adverse environments (Patel and Hillard 2006), and decreases immobility in rats in the forced swim assay (Gobbi et al. 2005) (also see Chap. 13).

In Chap. 10, Urigüen and García-Sevilla highlight findings from numerous experimental studies on the role of endocannabinoids and CB1rs in the modulation of brain monoaminergic systems: i.e., neuronal (spontaneous firing rate) activity and synthesis and release of the corresponding neurotransmitter. The authors also

discuss the effects of cannabinoid drugs on the activity of presynaptic monoaminergic receptors (autoreceptors and heteroreceptors) that regulate the synthesis and release of classic neurotransmitters and participate in the mechanisms of action of antidepressant drugs. Finally, the authors discuss the possible relevance of the ECS and CB1rs in the pathophysiology and treatment of major depression and schizophrenia, with a special focus on evidence from postmortem human brain studies.

Haj-Dahmane and Shen, in Chap. 11, review the current understanding of the cellular mechanisms by which the ECS modulates the function of the serotonergic system and how stress mediators regulate endocannabinoid signaling in the dorsal raphe nucleus (DRN). In the projection areas, endocannabinoids modulate serotonin transmission by suppressing serotonin release and regulating the expression and function of serotonin receptors (i.e., 5-HT_{1A} and 5-HT_{2A}). At the level of the DRN, endocannabinoid signaling controls the excitability of 5-HT neurons primarily by modulating the strength of glutamatergic and GABAergic inputs impinging on DRN 5-hydroxytryptamine (5-HT) neurons. The authors then highlight the discovery that DRN 5-HT can synthesize and release endocannabinoids in an activity-dependent "phasic" mode, which represents an additional mechanism that enables 5-HT neurons to fine-tune their electrical activity and control central 5-HT transmission. Finally, the authors discuss the implications of endocannabinoid signaling in the DRN as a key modulator and integrator mediating the homeostatic response to stress explaining that a dysfunction of endocannabinoid signaling in the 5-HT system could contribute to stress-related mood disorders. In Chap. 12, Gobbi discusses how CB1r agonists, antagonists, and FAAH inhibitors modulate the firing activity of 5-HT neurons located in the DRN. While the CB1 receptor agonist WIN 55,212-2 produces a bell-shaped curve, increasing 5-HT firing at low doses (0.1–0.3 mg/kg) and decreasing firing at higher doses (>0.3 mg/kg), the FAAH inhibitor URB597 produces a sigma-shaped curve, with a plateau at the highest doses tested (0.3 mg/kg). THC produces a mixed response on 5-HT firing activity with 26% of neurons showing an increase, 33% showing a decrease, and 42% showing no response. However, after 4 days, intraperitoneal (i.p.) injections of THC (1 mg/kg) produced a significant elevation of firing. These findings indicate that CB1r agonists and FAAH inhibitors interact with the 5-HT system and that these effects are related to emotional behaviors. Dogrul, in Chap. 13, reviews novel strategies for the development of novel therapeutics for pain such as, using peripherally restricted CB1 agonists, CB2 agonists or combining low doses of analgesic drugs from different pharmacological groups with the goal of developing additive or synergistic combinations with enhanced pain relief and reduced CNS effects.

O'Tuathaigh et al., in Chap. 14, review a large number of experimental studies examining the relationship between cannabis use, psychosis, and the influence of moderating environmental and genetic background factors. The authors explain that, although a minority of cannabis users develop subclinical symptoms or a clinical psychotic disorder, potential amplification of cannabis risk when interacting with genetic and other environmental risk factors may contribute to progression of the disorder. Focusing on clinical and preclinical studies, the authors elaborate on genetic data that provide convergent evidence for the notion of an interaction

between cannabis and individual genetic vulnerability, with a focus on genes encoding proteins implicated in DA signaling.

In summary, improving treatments for increasingly prevalent and devastating psychiatric and neurological illnesses is needed. Although challenges exist with medicinal cannabis, the potential for the development of compounds designed to modulate endocannabinoid levels or the use of synthetic cannabinoids with well-defined pharmacological properties may provide significant clinical benefit for psychiatric and neurological disorders. The potential for establishing cannabinoid-monoaminergic interactions as a novel target in the development of improved treatment strategies for psychiatric disorders is exemplified by the effectiveness of the CB1r agonist, nabilone, in the management of symptoms of post-traumatic stress disorder (Fraser 2009). Taken with recent evidence that the endocannabinoid and noradrenergic systems interact in stress-related memory consolidation (Hill and McEwen 2009; Campolongo et al. 2009), targeting interactions between these two systems may represent a novel approach for the treatment of stress-induced anxiety disorders. The potential for establishing cannabinoid-monoaminergic interactions as a novel target in the development of improved treatment strategies for neurological disorders is also promising but will require large-scale clinical studies to determine whether promising preclinical findings translate into new therapies.

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