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Cannabinoid Receptors Provide New Targets in Battling Anxiety

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Anxiety is a psychological/physiological state characterized by somatic, emotional, cognitive, and behavioral components, which affects roughly 40 million American adults above 18 years of age. In a clinical setting, humans are diagnosed with anxiety disorders through the professional administration of tests from the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV) [1]. Based upon certain criteria, clinicians can separate the observed behaviors into a variety of subtypes of anxiety including Generalized Anxiety Disorder (GAD), Panic Disorder, Post Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), or a Phobia of some kind [2,3]. While anxiety to some degree can be seen as relevant for survival, its persistence beyond situational arousal is generally considered pathological.

The etiology of anxiety disorders is unclear. It is known changes occur to the primary modulators of synaptic transmission including shifts in serotonin, nor-epinephrine, and dopamine release [4,5]. These same neuromodulators are associated with depression and many hypothesize these disorders are intertwined, with treatments for both disorders overlapping heavily [6]. For example, studies of mood in humans and rodents have shown severe or long-lasting stress can change the anatomical distribution of neuromodulators in the brain and therefore affect behavior [7]. Other investigations have shown individuals with certain anxiety disorders possess differences in neuroanatomical structures identified to play a crucial role in controlling memory and mood. Moreover, environmental factors, such as trauma or a major life-altering event, could trigger the emergence of anxious behavior in those who have an inherited susceptibility [3,8]. Treatment for anxiety usually consists of combined behavioral therapy with pharmacological manipulation using classical drugs including benzodiazepines, buspirone, selective serotonin or nor-epinephrine reuptake inhibitors, and older tricyclic antidepressants. These options have had limited success as their efficacy is highly patient dependant and the side effects are often intolerable, leading to discontinuation of therapy [9]. This suggests pharmacotherapies with better tolerability and broader efficacy must be developed, which is where the Endogenous Cannabinoid System (ECS) is poised to play a crucial role.

In recent years, the ECS has emerged as an important neuromodulatory system and has been heavily implicated in the regulation of anxious behavior [10-16]. Involvement of the ECS in the pathophysiology of anxiety provides a novel therapeutic avenue in the clinical treatment of this mental health disorder [14]. Although Cannabis sativa exists as a potent source of many natural cannabinoid ligands, most research conducted to date has focused on manipulating the ECS with synthetic compounds [10,11]. Controversy surrounding this plant in the United States has been the largest factor limiting the scope of research surrounding botanical cannabinoids, ultimately limiting their potential. With evidence continually accumulating concerning involvement of the ECS system in anxiety disorders, it is time to explore all avenues for modulating the neural substrates underlying this pathophysiological state.

The ECS is currently composed of cannabinoid receptor subtype 1 (CB1) and subtype 2 (CB2), which have been identified in the human genome and subsequently cloned in the early nineties [17]. Both CB1 and CB2 are metabotropic G-protein coupled receptors, which have dramatic effects on cellular activity by inhibiting andelyate cyclase and reducing the formation of cyclic-AMP [18]. During initial exploration of these receptors in rodents, it was generally assumed CB1 was primarily associated with neural tissue while CB2 was found predominantly in the periphery [19]. Thorough study demonstrated a presynaptic role for CB1 receptors in limiting neurotransmitter release at a majority of synaptic sites including noradrenergic, serotonergic, dopaminergic, glutamatergic, and GABAergic projections [20,21]. At the same time, CB2 was shown to play an important role in regulating the immune system, with high densities of CB2 receptors found in the spleen and in membranes of immune cells. With the advancement of molecular techniques in the recent years, CB2 has subsequently been identified in a variety of neural tissues, although at a much lower density than CB1 [22-24].

Endogenously, there are multiple lipophillic ligands with varying affinities for CB1 and CB2, as well as other receptors, such as the Transient Receptor Potential Vanilloid 1 (TRPV1) [15,21]. The two most common endogenous cannabinoids are 2-arachidonylglycerol (2-AG) and anandamide (ANA), which cannot be stored in vesicles and therefore are synthesized on demand from precursors. These molecules are produced in the post synaptic density then diffuse to pre synaptic targets and are eventually degraded through Fatty Acid Amide Hydrolase (FAAH) activity [25]. The low selectivity of endogenous cannabinoids gives rise to a complex pattern of activation states within the ECS, leading to difficulties in determining causality. To address this concern, antagonist molecules have been synthesized with 1000 fold greater selectivity for a particular receptor subtype. These have been used to great effect along with immunohistochemical and fluorescence assays in the determination of cannabinoid receptor localization. These studies indicate the ECS has a wide anatomical distribution with receptors reported throughout the cortex, striatum, amygdala, hippocampus, cerebellum, the thalamus and the hypothalamus [26]. Inhibition of neuronal excitation has been suggested as one of the roles for the ECS by protecting cells from hyper-excitation, which can lead to cell death. Due to the lipophillic nature of ECS ligands, there are both short and long term effects from changes in ECS tone due to the incorporation of signaling molecules into the cell membrane and subsequent breakdown [27]. This provides opportunities for the development of drugs to target this system as they will easily cross the blood brain barrier and can mediate long term effects, potentially reduce dosing intervals.

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Cannabinoid receptors have been identified in many regions that have also been associated with anxiety, such as the amygdala, hippocampus, ventro-medial forebrain, and peri aqueductal grey. However, interpretation of this localization and its effects on anxiety in rodents has been difficult [26]. Many studies of the effects of cannabinoids on anxiety in mammals show varied outcomes, which can often be attributed to differences in dose, drug, or experimental design. There have been major attempts to parallel classifications of behavior in humans to models of anxiety in rodents with limited success based upon the paradigm and behavior of interest. Measures of time spent in open versus enclosed environments, such as the elevated plus maze, have been used to great effect in the study of anxiety in rodents [28]. This method is based on the logic that rodents have evolved in an environment where enclosed spaces are relatively safe and anxiety free whereas the open spaces represent the opposite. Therefore, when an animal is placed in such as maze the time spent out in the open and time spent in enclosed spaces can be reported as a ratio representing the anxiety level of the animal [29]. Even though great attempts to standardize these methods have been made, interpretation of rodent behavior is still somewhat subjective. Clearly this situation requires remediation and further study should be dedicated to focusing the lens of experimentation on standardized models of anxiety in rodents.

There are several means of altering tone within the ECS, including direct agonism, direct antagonism, and blocking enzymatic pathways of cannabinoid degradation to increase endogenous levels [28,30]. Studies using direct agonists of the ECS including Delta -9-THC, WIN55-212,2, Anandamide, and others have shown that CB1 is responsible for the primary psychoactive effects associated with cannabis ingestion. The nature of the behavioral effects of these drugs on anxiety is biphasic, with low doses producing anxiolytic effects and anxiogenic effects emerging when high doses are administered [31]. In a mouse model of anxiety, the behavioral traits associated with anxiety can be ameliorated by injection of CB1 agonist into the dorsal hippocampus. Additionally, blockade of CB1 results in an anxiogenic response when CB1 antagonist AM251 is directly injected into the core of the amygdala or when it is administered systemically. The synthetic compound URB597 is an inhibitor of FAAH and when administered with anandamide can produce anxiety, but if either is given alone they produce anxiolytic effects [32]. Since CB1 is psychoactive, its use to treat anxiety is clouded due to its side effects, such as euphoria during the initial stages of blood plasma saturation. To this end, CB2 has been investigated as a potential anxiolytic target since it does not possess the psychoactive properties associated with CB1 activation [33]. Studies of CB2 and behavior have shown rodents with higher CB2 expression are resistant to anxiety and have differential responses to benzodiazepines, likely due to changes in GABAergic tone [34-36]. Studies of this receptor and its relationship to anxious behavior are still limited and must be further explored before any strong conclusions can be drawn. Since there is evidence the ECS system interacts with many different modulatory systems, including current anxiety treatments, exploration of this receptor family could open a new taxonomy of lipid-like drugs.

Collectively, this disparity in the literature suggests a rigorous reassessment of CB1 and the newly established CB2 must be performed in order to fully understand how this system modulates anxious behavior in rodents. This will provide new insight for modulation of the neuronal circuitry implicated in anxiety in a way that is truly distinctive from classical non-lipid medications and may prove to be more effective. Recent attempts to block CB1 receptors for the treatment of obesity triggered anxious and depressive behavior in human patients, ultimately leading withdrawal of the drug rimonabant from the European market [37]. This evidence in humans, in accordance with the robust supporting evidence in rodents, indicates CB receptors are involved in anxious behavior and should be further explored as a therapeutic target.

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References

1. Byers AL, Yaffe K, Covinsky KE, Friedman MB, Bruce ML (2010) High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. Arch Gen Psychiatry 67: 489-496.
2. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62: 617-627.
3. Bandelow B, Sher L, Bunevicius R, Hollander E, Kasper S, et al. (2012) Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and posttraumatic stress disorder in primary care. Int J Psychiatry Clin Pract 16: 77-84.
4. Chorpita BF, Barlow DH (1998) The development of anxiety: the role of control in the early environment. Psychol Bull 124: 3-21.
5. Zweifel LS, Fadok JP, Argilli E, Garelick MG, Jones GL, et al. (2011) Activation of dopamine neurons is critical for aversive conditioning and prevention of generalized anxiety. Nat Neurosci 14: 620-626.
6. Pynoos RS, Steinberg AM, Piacentini JC (1999) A developmental psychopathology model of childhood traumatic stress and intersection with anxiety disorders. Biol Psychiatry 46: 1542-1554.
7. Boureau YL, Dayan P (2011) Opponency revisited: competition and cooperation between dopamine and serotonin. Neuropsychopharmacology 36: 74-97.
8. Christianson JP, Ragole T, Amat J, Greenwood BN, Strong PV, et al. (2010) 5-hydroxytryptamine 2C receptors in the basolateral amygdala are involved in the expression of anxiety after uncontrollable traumatic stress. Biol Psychiatry 67: 339-345.
9. Farach FJ, Pruitt LD, Jun JJ, Jerud AB, Zoellner LA, et al. (2012) Pharmacological treatment of anxiety disorders: Current treatments and future directions. J Anxiety Disord 26: 833-843.
10. McLaughlin RJ, Gobbi G (2012) Cannabinoids and emotionality: a neuroanatomical perspective. Neuroscience 204: 134-144.
11. Crippa JA, Zuardi AW, Martín-Santos R, Bhattacharyya S, Atakan Z, et al. (2009) Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol 24: 515-523.
12. Haller J, Varga B, Ledent C, Freund TF (2004) CB1 cannabinoid receptors mediate anxiolytic effects: convergent genetic and pharmacological evidence with CB1-specific agents. Behav Pharmacol 15: 299-304.
13. Ashton CH, Moore PB (2011) Endocannabinoid system dysfunction in mood and related disorders. Acta Psychiatr Scand 124: 250-261.
14. Busquets-Garcia A, Puighermanal E, Pastor A, de la Torre R, Maldonado R, et al. (2011) Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. Biol Psychiatry 70: 479-486.
15. Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O (2002) Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology (Berl) 159: 379-387.
16. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, et al. (2011) Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol 25: 121-130.
17. Hill AJ, Williams CM, Whalley BJ, Stephens GJ (2012) Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther 133: 79-97.
18. Witkin JM, Tzavara ET, Nomikos GG (2005) A role for cannabinoid CB1 receptors in mood and anxiety disorders. Behav Pharmacol 16: 315-331.
19. Rutkowska M, Jamontt J, Gliniak H (2006) Effects of cannabinoids on the anxiety-like response in mice. Pharmacol Rep 58: 200-206.
20. Zarrindast MR, Mahboobi S, Sadat-Shirazi MS, Ahmadi S (2011) Anxiolytic-like effect induced by the cannabinoid CB1 receptor agonist,

arachydonilcyclopropylamide (ACPA), in the rat amygdala is mediated through the D1 and D2 dopaminergic systems. J Psychopharmacol 25: 131-140.

21. Moreira FA, Aguiar DC, Terzian AL, Guimarães FS, Wotjak CT (2012) Cannabinoid type 1 receptors and transient receptor potential vanilloid type 1 channels in fear and anxiety-two sides of one coin? Neuroscience 204: 186-192.

22. Pertwee RG (2006) Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 147: S163-171.

23. Onaivi ES, Ishiguro H, Gong JP, Patel S, Perchuk A, et al. (2006) Discovery of the presence and functional expression of cannabinoid CB2 receptors in brain. Ann N Y Acad Sci 1074: 514-536.

24. Onaivi ES (2006) Neuropsychobiological evidence for the functional presence and expression of cannabinoid CB2 receptors in the brain. Neuropsychobiology 54: 231-246.

25. García-Gutiérrez MS, Manzanares J (2011) Overexpression of CB2 cannabinoid receptors decreased vulnerability to anxiety and impaired anxiolytic action of alprazolam in mice. J Psychopharmacol 25: 111-120.

26. Campos AC, Guimarães FS (2008) Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology (Berl) 199: 223-230.

27. Rossi S, De Chiara V, Musella A, Sacchetti L, Cantarella C, et al. (2010) Preservation of striatal cannabinoid CB1 receptor function correlates with the antianxiety effects of fatty acid amide hydrolase inhibition. Mol Pharmacol 78: 260-268.

28. Rodgers RJ, Evans PM, Murphy A (2005) Anxiogenic profile of AM-251, a selective cannabinoid CB1 receptor antagonist, in plus-maze-naïve and plus-maze-experienced mice. Behav Pharmacol 16: 405-413.

29. García-Gutiérrez MS, Manzanares J (2010) The cannabinoid CB1 receptor is involved in the anxiolytic, sedative and amnesic actions of benzodiazepines. J Psychopharmacol 24: 757-765.

30. Haller J, Barna I, Barsvari B, Gyimesi Pelczer K, Yasar S, et al. (2009) Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology (Berl) 204: 607-616.

31. Zarrindast MR, Sarahroodi S, Arzi A, Khodayar MJ, Taheri-Shalmani S, et al. (2008) Cannabinoid CB1 receptors of the rat central amygdala mediate anxiety-like behavior: interaction with the opioid system. Behav Pharmacol 19: 716-723.

32. Carvalho AF, Van Bockstaele EJ (2012) Cannabinoid modulation of noradrenergic circuits: implications for psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 38: 59-67.

33. Moreira FA, Grieb M, Lutz B (2009) Central side-effects of therapies based on CB1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. Best Pract Res Clin Endocrinol Metab 23: 133-144.

34. Naderi N, Haghparast A, Saber-Tehrani A, Rezaii N, Alizadeh AM, et al. (2008) Interaction between cannabinoid compounds and diazepam on anxiety-like behaviour of mice. Pharmacol Biochem Behav 89: 64-75.

35. Urigüen L, García-Gutiérrez MS, Manzanares J (2011) Decreased GABAA and GABAB receptor functional activity in cannabinoid CB1 receptor knockout mice. J Psychopharmacol 25: 105-110.

36. Moreira FA, Aguiar DC, Guimarães FS (2007) Anxiolytic-like effect of cannabinoids injected into the rat dorsolateral periaqueductal gray. Neuropharmacology 52: 958-965.

37. Horder J, Browning M, Di Simplicio M, Cowen PJ, Harmer CJ (2012) Effects of 7 days of treatment with the cannabinoid type 1 receptor antagonist, rimonabant, n emotional processing. J Psychopharmacol 26: 125-132.