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How the Allostatic Load can Work to Desensitize the CB1 Receptor and How Anandamide and the Fatty Acid Amide Hydrolase Can Work to Influence Emotional States

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Abstract

This paper provides an interpretation of how the CB1 receptor (CB1R) can be negatively impacted when the allostatic load is achieved. It describes how anandamide and the fatty acid amide hydrolase (FAAH) can work to influence an overall emotional state. As we interact with external stimuli we can perceive this interaction as either being positive, neutral or negative. In the presence of a negative or positive event we can experience what is called the "allostatic load." In some instances, when the allostatic load is achieved, the CB1R can become desensitized. The CB1R becomes desensitized when it encounters a frequent response, inadequate response or failure to shut off the response to the event. If the allostatic load is not achieved, then the response would ultimately be encoded in the short-term memory. If the allostatic load is achieved, then the event can be stored in the long-term memory. Various mental states could be a result of this process of desensitization. The levels of anandamide (CB1R agonist) and FAAH(anandamide antagonist) can be compared to positive, neutral and negative events. These chemical releases could also lead to the overall emotional responses that we arrive at when facing a stimui. In conclusion, I find there to be a relationship between the CB1R, anandamide, FAAH and emotional expression. I hypothesize that the CB1R can become desensitized and can influence our overall emotional state.

Keywords: CB1 Receptor, Desensitize, Allostatic load, Fatty acid amide hydrolase.

A study on "Plastic and Neuroprotective Mechanisms Involved in the Therapeutic Effects of Cannabidiol in Psychiatric Disorders" [1] it stated that CBD lowers the negative cognitive and psychoactive consequences of THC while preserving its beneficial actions**.** If CBD reduces that effect, then it may prove to be a reliable treatment in psychological disorders. There are many types of cannabis strains sativa, sativa hemp, and indica. The sativa has an anti-depressant effect, the indica has a depressant effect and the sativa hemp has a neutral effect. When combined they effectively treat pain causing a euphoric effect. This relationship would need to be investigated further, however.

So, what if those strains hold the keys to regulating various emotional states? What if these strains have differing effects on emotion? These questions should be addressed. Cannabinoid receptors are part of the ECS and are mainly located in the brain, but are also in the liver, kidneys and lungs. These are the same organs affected during hypovolemic shock. There are two known cannabinoid receptors: CB1 and CB2 receptors. CB1 receptors are found in places such as the brain and organs. CB2 receptors are found in places such as the immune system and spinal column. The ECS seeks to balance and normalize the affected

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areas, while ultimately trying to protect them from damage. It seeks to normalize the hypothalamic-pituitary-adrenal axis (HPA) during trauma. In a study titled: "The Role of the Endocannabinoid System in the Regulation of Hypothalamic Activity" [2] it was found that the ECS is known to regulate the HPA. This axis is responsible for neuroendocrine adaptation to stress responses. This adaptation leads to the release of adrenaline, cortisol and other chemical messengers. Anandamide is known to be released with cortisol. It is also known as the "feel-good" chemical experienced in a "runners' high." Anandamide is a natural cannabinoid produced in our body and is responsible for attaching to cannabinoid receptors. It is the agonist in this case. In response to shock, the HPA releases chemical messengers. These releases occur during hypovolemic shock, which is a condition that occurs when 20 percent or more of the body's blood or fluid supply is lost and is considered life threatening. When sustaining hypovolemic shock, the body can lose too many fluids, and bodily organs can begin to fail. Organs that may be affected during hypovolemic shock include the brain, liver, kidneys and lungs. When experiencing shock, mechanisms in the body adapt to the stressor in an attempt to normalize functions. This attempt to normalize is known as "homeostasis." In a study titled "Stress, Adaptation, and Disease: Allostasis and Allostatic Load" [3] stated that during shock, the Activation of Neural, Neuroendocrine and Neuroendocrine-immune mechanisms change when encountering potentially stressful events through the production of mediators such as adrenalin, cortisol and other chemical messengers. These changes are known as allostasis. The study continues, stating that allostasis is an essential component of regulating homeostasis and that it can become overactive. This is known as the allostatic load. Also, the study states that the "allostatic load" is reached when one of the following criteria are met: frequent activation of allostatic systems, failure to shut off allostatic activity after the stress, and inadequate response of allostatic systems, which leads to elevated activity of other normally counter-regulated allostatic systems after stress [3]. In hypovolemic shock, when the allostatic load has been reached, the chemical messengers released into the circulatory system would be hindered due to vascular resistance. Vascular resistance, in hypovolemic shock, is attributed to the loss of blood or fluid. The vessels constrict, thus inhibiting the bodies attempt to normalize function. When the fluid or blood loss is returned, vasodilation occurs. This allows the chemical messengers, such as the agonist anandamide to flow unrestricted again. However, at this point, the ECS has begun to normalize and may not need these chemical messengers anymore. One such chemical that may no longer be essential could be cortisol, and anandamide, as body functions stabilize. A study conducted on "Endocannabinoid Signaling and the Hypothalamic-Pituitary-Adrenal Axis" [2] stated that when activation of the CB1 receptor occurred, it promoted the return of the HPA axis to non-stressed levels. This would imply that if non-stressed levels where achieved, then activation would not be necessary. If activation is not necessary, then the CB1Rs would experience decreased responsiveness due to receptor overload, which would lead to receptor desensitization. They no longer need what they are receiving. The ECS is said to be the driving force behind homeostasis within the sympathetic and parasympathetic nervous systems. Both of these systems seek to normalize functioning while being monitored by the ECS. A study titled "Neuroendocrine System and the Autonomic Nervous System" [4] stated that both of these systems are the executing force controlled by the hypothalamus. In this study, it says that the autonomic nervous system is responsible for transmitting organ function back to the brain so that it can regulate these areas. If organ function is affected during hypovolemic shock, and the ECS is unable to maintain homeostasis, then the system could reach a state of allostatic load. The ECS is signaling for a hypothalamic-pituitary neurosecretion response, but it has the insufficient means to transport these secretions through the circulatory system as they occur. Many symptoms of shock show similarities in mental disorders such as PTSD, depression, anxiety disorder and bipolar disorder. These symptoms include: agitation, restlessness, anxiety, altered mental status, altered mental states, rapid or slowing heart rate, labored or irregular breathing, reduced body temperature, dilated pupils and falling blood pressure. It has been found that when the CB1R is given an antagonist, mental health problems can arise. In a study conducted on the "Efficacy and Safety of the Weight-Loss Drug Rimonabant" [5] randomized human trials found that the CB1R antagonist rimonabant had significant adverse psychiatric effects. In this study, it was found that patients experienced changes in thought patterns such as anxiety, depressed mood and even suicide. This would lead one to assume that if the CB1R is desensitized, then mental illness may arise. This would cause a decrease in the responsiveness of these receptors. When vasodilation occurs, the body is flooded with chemical messengers that are no longer needed. Since the ECS has regained balance, a system imbalance may occur because the overabundance of chemical messengers is no longer needed. This imbalance to the ECS could lead to the development of various mental disorders or altered mental states such as PTSD, depression, anxiety and bipolar disorder.

A study on "The Role of the Endocannabinoid System in the Regulation of Endocrine Function and in the Control of Energy Balance in Humans" [6] stated that the endocannabinoid system has been recently attributed to being an important modulatory system in the operation of the brain in the endocrine and immune systems. The study goes on to state that it would seem to have a very important regulatory role in the chemical release of hormones related to reproduction and stress responses. This led to my interpretation of how the allostatic load can influence the CB1R, leading to its damage or desensitization. The ECS is responsible for creating homeostasis in the sympathetic and parasympathetic nervous systems. The ECS will activate during a stressful event and stay active until it achieves balance. If it cannot maintain this delicate balance, it will become an imbalanced system. This imbalance is known as the allostatic load. Only one of the following criteria need to be met to reach the allostatic load of the CB1R. The ECS signals homeostasis due to a traumatic event caused from either **frequent exposure** to a stressful event, an **inadequate response** to a stressful event or **failure to**

shut off when a stressful event occurs. Refer to Figure 1A for visual reference. I hypothesize that each situation has a different effect on the CB1R, leading to its desensitization. The influence each occurrence has on the CB1R is as follows: A **frequent response** to a stressful event leads to desensitization of the CB1R, causing it to become overactive. An **inadequate response** to a stressful event leads to CB1R desensitization, causing an under-active CB1R. A **failure to shut off,** or "**flooding,**" occurs when a stressful event leads to CB1R desensitization. This produces an imbalance that leads to CB1R flooding followed by a recovery period where the CB1R becomes deficient. When a frequent response to a stressful event occurs, the hypothalamic-pituitary-adrenal axis (HPA) is frequently accessed. It occurs due to frequent chemical releases within the HPA during exposure to more than one stressful event, which leads to an overstimulated CB1R and ultimately its desensitization.

So, can this be regulated by supplementing this overstimulation with the neutrality of the sativa hemp and indica plant? With this combination, you might get a non-psychoactive, depressant effect, which could prove reliable in supplementing the overstimulation. An example of an inadequate response occurs when vascular constriction does not allow an HPA release to move through the circulatory system. This could be experienced during hypovolemic shock. If desensitization leads to a deficiency, then would the sativa hemp and sativa strain work to balance this deficiency by creating a non-psychoactive, anti-depressant effect? A failure to shut off after a stressful event occurs when flooding from the HPA takes place due to the ECSs inability to regain equilibrium. This could result from frequent drug use (flooding) or lead to biPolar disorder (flooding, deficiency). Could the sativa hemp plant be the neutral plant responsible for fixing CB1R desensitization in this case? This may need to be looked into further. A chart is provided for visualizing the following conclusions. The above results are dependent on the state of allostatic load being met. The resulting mental state is depicted through the level of CB1R desensitization and what type of desensitization is sustained. PTSD and anxiety could arise from frequent exposure to a stressful stimuli or overstimulation of the CB1R. Depression could arise from an inadequate response to stressful stimuli resulting in a CB1R deficiency. Bipolar disorder could arise from the failure to shut off to a stressful event, resulting in an overstimulated CB1R followed by a deficiency. This needs to be investigated further, however.

Expanding on the previous hypothesis, I formed another one on the relationship between anandamide and FAAH and how those levels may affect our emotional states. This hypothesis involves emotional regulation in the presence of positive, negative and neutral external stimuli which lead to emotional responses. How we regulate emotional responses is an unanswered question in neuroscience. When we interact with external stimuli it results in a behavioral response. A study conducted on "The Effects of External Stimuli on the Emotional-Aversive Response Evoked by Intrahypothalamic Carbachol Injections" [7] observed that cats' reactions to positive and neutral stimuli produced a very opposite emotional response. The study tested the effects of threatening stimuli (seeing a barking dog) or neutral stimuli (a flash and tone) on the emotional-aversive responses, when injected with carbachol. All

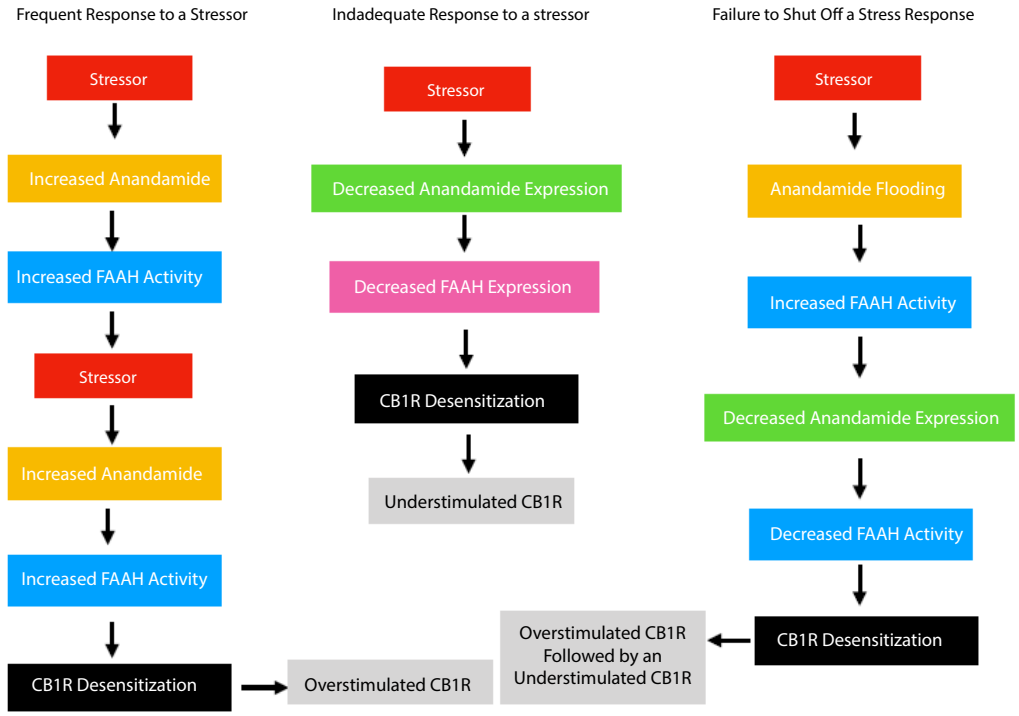

Figure 1: This figure represents the allostatic load being reached during a stressful event and how it can ultimately affect the function of the CB1 receptor. A **frequent response** to a stressful event leads to desensitization of the CB1R causing it to become overactive. An **inadequate response** to a stressor leads to CB1R desensitization causing an underactive CB1R. A **failure to shut off,** or "flooding," occurs when reacting to a stressful event leads to a CB1R imbalance, causing an overactive CB1R followed by a recovery period where the CB1R becomes underactive.

of the threatening stimuli led to a significant increase in vocalization in the cats. In comparison, the neutral stimuli of comparable intensity produced no response. When we are presented with external stimuli the ECS controls the releases of anandamide and FAAH in our body through the HPA. This is why it is important to understand the importance of this systems function, which is homeostasis. In a study on the "Modulation of Anxiety through a Blockade of Anandamide Hydrolysis" [8] when tetrahydrocannabinol was administered to humans it produced subjective responses that were controlled by the CB1Rs. This indicated that they might contribute to emotional control. If cannabis has been found to produce the responses indicated above, then the various strains of cannabis may hold the keys to providing a safe means to regulate mood disorders.

In another study, on how a "CB1R Deficiency Decreases Wheel-Running Activity: Consequences on Emotional Behaviours and Hippocampal Neurogenesis" [9] it was stated that chronic voluntary wheel-running activity has been observed in an overstimulated central CB1R in mice; and also, that the pharmacological results indicated that the CB1R may be involved in wheel-running behavior and in running induced neurogenesis in the hippocampus. The endocannabinoid system is in charge of maintaining homeostasis in the sympathetic and parasympathetic nervous systems. The hippocampus relays the encoded incoming emotional responses to the sympathetic nervous system, which controls the CB1 receptors (CB1R). The CB1Rs are responsible for the expression of those encoded emotional responses. In a study on the "Potential Therapeutic Value of a Novel FAAH Inhibitor for the Treatment of Anxiety" [10] it was found that when the new enol-carbamate ST4070 drug inhibited FAAH in vivo, it was observed that it enhanced endocannabinoid signaling in the brain regions engaged in emotional control. So, does this indicate that anandamide was influencing the expression of the encoded emotions through its interaction with the CB1Rs leading to increased stimulation due to the inactivity of FAAH? If true, then varying levels of both anandamide and FAAH lead to various behavioral responses. This could cause the unacceptable behavior resulting in many cognitive disorders. A cognitive disorder is basically the presentation of frequent abnormal behaviors. Anandamide is known as the "feel good" chemical and agonist that binds to the CB1R. The fatty acid amide hydrolase (FAAH) is an antagonist of anandamide. A study conducted on the "Interactions Between Anandamide and Corticotropin-Releasing Factor Signaling Modulate Human Amygdala Function and Risk for Anxiety Disorders: An Imaging Genetics Strategy for Modeling Molecular Interactions" [11] suggested that interactions between the anandamide and corticotropin-releasing factor (CRF1) receptor extinction showed a reduction in both anandamide and FAAH. If anandamide is released with CRF1 and binds to the CB1R to signal homeostasis in the amygdala, then the desensitization of the CB1R could produce a constant state of stress and hinder anandamides ability to signal the down regulation of the amygdala. CB1R desensitization could explain the occurrence of adrenal fatigue syndrome. It could also explain the similarities that exist in disorders like anxiety, ptsd, bipolar and schizophrenia. Given the above argument, I hypothesize that increases and/or decreases in anandamide and FAAH expression, directly influence which emotional states are created through their interaction with each other, and that they work to influence the CB1R. Also, the type of stimuli being faced, whether positive, negative or neutral, would influence the levels of anandamide and FAAH being expressed. The previous model for allostatic load can be used in relation to this hypothesis. In this instance, the following analogy was made:

- When in the presence of negative stimuli, an increase in anandamide and increase in FAAH expression would result in the expression of fear and/or anger. This behavior may occur because the agonist and antagonist are competing and the CB1R is frustrated, if you will.
- When in the presence of negative stimuli, A decrease in anandamide and a decrease in FAAH expression would result in the expression of sadness and/or disgust. This behavior may occur because the CB1R is missing the much-needed interaction that it is looking for.
- When in the presence of positive stimuli, an increase in anandamide and a decrease in FAAH expression would result in the expression of joy and/or surprise. This behavior may occur because the agonist is stimulating the CB1R causing it to "feel good."
- When in the presence of neutral stimuli, anandamide and FAAH expression would remain unaffected or neutral resulting in trust. This may occur because the CB1R is comfortable as it is in its preferred balanced state.

In conclusion, I have explained my two hypotheses and listed analogies of what may be occurring in the ECS, CB1Rs, anandamide (CB1R agonist) and FAAH (anandamide antagonist). I described how allostatic load can work to desensitize the CB1Rs when facing a single or recurring stressful event. I have provided a chart for reference and it may be found that various altered mental states fit well with the model. I have covered the function of the various cannabis strains and their corresponding effects and possible therapeutic values. How the ECS works to influence the emotional states through chemical messengers was explained. I also provided two different, but connected, hypotheses that are affected by the levels of both anandamide and FAAH respectively. Although these are hypothesized values, the system will seek balance; and when we are talking about the ECS, CB1Rs, anandamide, FAAH, homeostasis, and emotions, balance may be of relevance since we seek it through this system. Further analysis would be necessary, however.

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