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Mini Review

Homeostasis: Hormones, Endocannabinoid Ligand Polarity, Breastfeeding and Infertility

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Abstract

This paper is an extension of two previously published works titled: "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" and "CB2R Desensitization and Long and Short-Term Memory Storage". The previous research was initiated by asking the question: How does hypovolemic shock resulting from severe dehydration contribute to the development of post-traumatic stress and bipolar disorder? The vascular system was of relevance. How vasoconstriction might hinder the flow of chemical messengers in the body and contribute to a decrease in the flow of energy molecules in the bloodstream was of interest. Vasoconstriction could contribute to a reduction in the flow of energy molecules and negatively impact emotion and immune function. In this paper, the interaction between the chemical hormones, estrogen and testosterone and their relation to the endocannabinoid system was investigated. It was found that when estrogen binds to the estrogen receptor, nitric oxide is expressed. Nitric oxide can be found to influence signaling activities and could functionally reverse the polarity of the endogenous ligands, anandamide and 2-arachidonoylglycerol. If the polarity is reversed, then ANA could function to bind to and down regulate at the CB2 receptor and 2-AG could function to bind to and up regulate at the CB1 receptor. This signaling process could function to provide homeostasis. The functionality of the ligands was related to breast feeding, emotional development and age related hormonal changes. The hormonal impact on mood was also discussed, but will need to be researched further. In conclusion, it was found that the endocannabinoid system, sex hormones, nitric oxide expression and the vascular system all have a mutual relationship. Vasoconstriction could indicate the expression of testosterone or a testosterone dominant ligand, like anandamide induces vasoconstriction in order down regulate and control the flow of energy producing molecules. In retrospect, vasodilation could occur when estrogen is expressed or an estrogen dominant ligand, like 2-AG is expressed and vasodilation could increase the flow of energy producing molecules in the blood. If vasoconstriction occurs, then nitric oxide may be depleted or reduced and the flow of energy producing molecules in the blood could be reduced. This could result in a decrease of energy, decrease in mood and/or a compromised immune system. If the polarity of ANA and 2-AG change, then ANA could down regulate a rest and digest response and 2-AG could indicate a down regulated adrenal response. This change in the polarity could be responsible for changing signaling activities and maintaining homeostasis between the sympathetic and parasympathetic nervous system. These relationships will all need to be investigated further, however.

Keywords: *Homeostasis; Endocannabinoid System (ECS); Breastfeeding; Infertility*

Introduction

The endocannabinoid system (ECS) is a complex and relatively new system that was first discovered in 1992. This system contains two primary receptors, the CB1 and CB2 receptors and two primary ligands, anandamide and 2-arachidonoylglycerol. The ECS is known to have a strong connection to the human sex organs in both men and women. Also, endogenous cannabinoids are found in breast milk

and can be passed from mother to child. This paper is intended to analyze and investigate the current available data and to provide a perspective on how the chemical hormones can influence the polarity of the endogenous ligands in the endocannabinoid system. It will explain how vasoconstriction and vasodilation can work to increase and decrease the flow of signaling molecules in the body in order to provide homeostasis. It will also provide a relationship between the endogenous ligands contained in maternal breastmilk and provide an interpretation of how the expression of these ligands could impact the emotional state of the baby during development. Finally, it will explain how variances in estrogen and/or testosterone can influence emotional states throughout the life cycle by influencing the expression of nitric oxide and ligand polarity in order to provide homeostasis.

Methods

This study was conducted and compared against the current available research and is an extension of two previously published works titled:

1. Terry W (2019) 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. Sch J Appl Sci Res Vol: 2, Issu: 2 (18-22).
2. Terry W (2019) CB2R Desensitization and Long and Short-Term Memory Storage. Sch J Appl Sci Res Vol: 2, Issu: 2 (13-17).

The studies where initiated by questioning how hypovolemic shock from dehydration can cause post-traumatic stress and bipolar disorder. The endocannabinoid and vascular system where both studied. Also, cannabidiol was of interest due to the therapeutic value and was studied and found to attach to the estrogen receptor. In conducting further research it was discovered that when estrogen attached to the estrogen receptor that it triggered the release of nitric oxide. The study was concluded when it was found that nitric oxide expression can influence the polarity of the ligands and influence their binding activities to receptors in the g-coupled receptor family. These findings where related to the sex hormones, nitric oxide, differences in mood and the role of breastfeeding in relation to the findings.

Discussion

Estrogen and testosterone are chemical hormones responsible for determining the sex characteristics of a child. Testosterone is a "stress" hormone and can be associated to an "up-regulatory" or adrenal response. Estrogen is a "rest and digest" hormone and can be associated to a "down-regulatory" or energy metabolizing response. In the study "Effects of Endogenous Testosterone and Estradiol on Sexual Behavior in Normal Young Men [1]", found that in men who experienced a reversible, gonadal steroid deficiency became hypogonadal within one week and experienced increased aggression, which could be related to the decrease in testosterone expression. While men produce more testosterone then women, they produce less estrogen. When a small change in the dominant hormone (i.e. testosterone or estrogen) occurs, it can influence a long-term emotional state or illness. This can be seen throughout the life cycle in puberty, pregnancy and old age. In the study "Surging Hormones: Brain-Behavior Interactions During Puberty (Peper and Dahl 2013)", indicated that hormone changes during puberty can create small changes in behavior, which can eventually lead to high-impact changes in behavioral patterns over time. In another study titled: "Symptoms in the Menopausal Transition: Hormone and Behavioral Correlates [2]", indicated that upon the transition to menopause that headache, irritability and mood swings decreased. This could be influenced by an increase in the expression of testosterone. A small decrease in estrogen could mean a large increase in testosterone, but this will need to be investigated further. In the study "Androgenic Hormones and Aging-The Link with Female Sexual Function [3]", it indicated that as females age, the androgen levels decrease. Emotions that could be associated to estrogen can include sadness, surprise and fear. Sadness can be associated to low estrogen. In the study on "Estrogen, Stress and the Brain: Progress Toward Unraveling Gender Discrepancies in Major Depressive Disorder (Shansky, 2014)", estrogen was associated to major depression and the study expressed that women are twice as likely to experience depressive episodes. In opposition, emotions that can be associated to testosterone can include anger, disgust and happiness. In the study "Happiness and Health: The Biological Factors-Systematic Review Article [4]", it found a relationship between happiness and the up-regulatory chemical messengers, dopamine, serotonin, norepinephrine, endorphin and epinephrine, which can be associated to an adrenal response. The emotional impact of testosterone and estrogen would need to be investigated further, however.

Nitric oxide production can influence the polarity and binding activities within the endocannabinoid system. In the study "Gating the Polarity of Endocannabinoid-Mediated Synaptic Plasticity by Nitric Oxide in the Spinal Locomotor Network (Song, Kyriakatos and El Manira, 2012)", it found that endocannabinoids and nitric oxide can become excited and shift polarity in the spinal locomotor network. The endogenous cannabinoids; ANA and 2-AG both have an affinity with the CB1 and CB2 receptors in the body. Estrogen and testosterone can either increase or decrease the expression of nitric oxide. In the study titled: "Estrogen Induces Nitric Oxide Production via Nitric Oxide Synthase Activation in Endothelial Cells (Nevzati, Shafighi, Bakhtian, Treiber, Fandino, and Fathi, 2015)", it found that estradiol influences the increased expression of nitric oxide in cerebral and peripheral endothelial cells *in vitro*.

In another study titled: "Up-Regulation of Nitric Oxide Synthase by Estradiol in Human Aortic endothelial Cells [5]", it indicated that nitric oxide synthase can be regulated by Estrogens in the human body. Estrogen can increase nitric oxide, while testosterone can decrease the expression. In the study "Testosterone Inhibits Expression of Inducible Nitric Oxide Synthase in Murine Macrophages [6]", it stated that testosterone led to a decline in nitric oxide levels, which could lead to an elevated risk of infection.

The endocannabinoid system can control the balance between the up-regulatory and down-regulatory processes that occur within the body. The endogenous cannabinoid ligands, N-arachidonoylethanolamine (ANA) and 2-Arachidonoylglycerol (2-AG), can monitor and control the signal transduction pathways responsible for up-regulating and down-regulating the body. In a study titled: "Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System (Shenglong and Ujendra, 2018)", it stated that cannabinoids modulate signal transduction pathways associated with several pathophysiological conditions. ANA can be associated to an adrenal response and stress. In a study on the "Expression and Function of Endocannabinoid Receptors in the Human Adrenal Cortex (Ziegler, Mohn, Lamounier-Zepter, Rettori, Bornstein, Krug and Ehrhart-Bornstein, 2009)", it related ANA and the CB1 to the human adrenal cortex and adrenocortical steroid release. 2-AG can be associated to the rest and digest activities. In a study on "2-Arachidonoylglycerol Signaling in Forebrain Regulates Systemic Energy Metabolism [7]", it suggested that 2-AG can bind to the CB1 receptor and regulate the forebrain neural circuits involved in the control of energy dissipation. ANA and 2-AG can bind to either the CB1 or CB2 receptor and can create homeostasis between the sympathetic and parasympathetic nervous system. In a study on the "Dual Blockade of Fatty Acid Amide Hydrolase (FAAH) and Monoacyl Glycerol Lipase (MAGL) Identifies Behavioral Processes Regulated by Endocannabinoid Crosstalk *in vivo* (Long, Nomura, Vann, Walentiny, Booker, Jin, Burston, SimSelley, Lichtman, Wiey and Cravatt, 2009)", it was found that ANA and 2-AG signaling pathways can interact to regulate behavior processes in vivo and that CB1 receptor agonists could be a therapeutic target for behavior modification.

Oxytocin, vasopressin, ANA and 2-AG could be associated to homeostasis, stress and recovery. Oxytocin is used to induce labor and is called the "cuddle molecule" and vasopressin is used to increase blood pressure. Oxytocin could function to metabolize energy, while vasopressin could function to produce energy. ANA, 2-AG, oxytocin and vasopressin can all produce a state of anxiety. Anxiety could be experienced as the polarity of ANA, 2-AG, oxytocin and vasopressin change. The Change in affinity could produce anxiety as the testosterone dominant molecules (ANA and vasopressin) can work to reduce or counteract a rest and digest response on the estrogen dominant side. This action could function to reduce depression by increasing the blood flow and the transport of signaling molecules in the blood. Also, anxiety could result when the estrogen dominant molecules (2-AG and oxytocin) work to metabolize energy and down-regulate a response on the testosterone dominant side. ANA and vasopressin can be associated to testosterone and can work to reduce a down-regulatory response by increasing the blood flow, decreasing inflammation and inhibit the collection of blood platelets. 2-AG and oxytocin can be associated with estrogen and could work to decrease the blood flow by increasing inflammation and the collection of blood platelets within the vascular system.

A relation could be made between the endocannabinoid system and breastfeeding. ANA, 2-AG, oxytocin and vasopressin could function in the feeding and developmental processes. In a study on the "Detection of the Endocannabinoid Metabolome in Human Plasma and Breast Milk (Durham, Wood, Vadivel, Makriyannis and Lammi-Keefe, 2013)", it indicates that endogenous cannabinoid ligands

are contained in breast milk. In another study on the "Effect of Breast-Feeding on Concentration of Nitric Oxide in Breast Milk [8]", it found that breastfeeding increases the levels of nitric oxide in breast milk and the group that did not breastfeed had significantly lower levels of nitric oxide. Also, in a study on "Non-Enzymatic Nitric Oxide Generation in the Stomachs of Breastfed Neonates (Iizuka, Sasaki, Oishi, Uemura, Koike and Shinozaki, 1999)", found that breastmilk induced the production of nitric oxide in the stomach of newborn children and that nitric oxide was present on the milk surface in vitro. The mother could be contributing to the development of the babies emotional state by providing signaling molecules as well as nitric oxide to the baby. These signaling ligands can influence the broad range of emotions, which could be developed during and after gestation. The endogenous ligands expressed can provide stress and rest and digestive responses and signal homeostasis in the offspring. Vasopressin could function in the secretion of the breast milk. It could signal lactation by reducing the inflammation within the breast leading to the secretion of the breast milk. ANA is associated to stress and could function to pass stress from the mother to the child and stimulate vasoconstriction and blood platelet aggregation in the vascular system. 2-AG is associated to the rest and digestive activities and could function to signal a vasodilation response to increase the flow of signaling messengers and to relax the flow of energy signaling molecules to provide rest and to aid in digestive functioning during the developmental process. Finally, oxytocin could be responsible for signaling homeostasis. This push and pull relationship between ANA and 2-AG could be neutralized through the expression of oxytocin. Oxytocin or the "cuddle molecule" could have a homeostatic function, but this would have to be researched further [9,10].

Conclusion

The evidence suggests that anandamide is a testosterone dominant ligand that can increase the stress load, while 2-AG is an estrogen dominant ligand that can decrease the stress load. 2-AG can bind to and down regulate the CB1 receptor and could function to deliver white blood cells and aid in rest and digestive activities during homeostasis. The CB1 receptor is responsible for the flow of energy molecules with in the vascular system. It controls the flow of energy producing molecules through platelet aggregation and vasoconstriction. The polarity of ANA and 2-AG can both be influenced when nitric oxide is expressed. By reversing the polarity of the ligands, 2AG could function to bind to the CB1 receptor and increase the flow of signaling molecules in the blood through vasodilation and by inhibiting platelet aggregation. Also, ANA could function to reduce a rest and digestive response by gaining affinity and binding to the CB2 receptor. ANA could function to bind to the CB2 receptor and decrease the flow of rest and digestive or energy metabolizing molecules in the blood through vasoconstriction and increase platelet aggregation in the vascular system. The nitric oxide that is expressed with estrogen can change the polarity in the ligands, while testosterone could reduce the expression of nitric oxide. A relationship was made between the endogenous cannabinoid ligands, breast milk and how these could functionally provide stress, rest and homeostasis as well as contribute to the development of the emotional range or stress capacity of the baby. This will need to be investigated further, however. Also, if the affinity of ANA and 2-AG can be changed through the expression of nitric oxide, then an overactive adrenal response could be down-regulated as 2-AG experiences a shift in polarity, gains affinity, and binds to the CB1 receptor to reduce the stress associated with infertility or age related issues in men, women and children. Also, how a small shift in the dominant hormone can have a magnifying effect on the less dominant hormone in a man or woman will need to be investigated further. This magnifying effect could explain why menopause has underlying similarities to the expression of testosterone such as loss of hair, hot flashes, night sweats, weight gain and slowed metabolism to name a few. Finally, the endocannabinoid systems influence on the vascular system is of interest. During a stress response the flow of energy molecules is hindered due to the lack of nitric oxide released on the testosterone dominant side. When the vascular system is constricted the flow of energy molecules is disrupted. Since the flow is constricted these signaling molecules may not flow properly and could influence mood and lead to the formation of disease. These findings indicate that our mood may be directly impacted through our vascular system, which relies on the expression of nitric oxide in the endothelium to create vasodilation or vasoconstriction. Testosterone could be the hormone associated with heat and energy molecules in the body. Estrogen could be the hormone associated with the cooling or energy metabolism and fat storage in the body. The influence that estrogen has on the expression of nitric oxide and how nitric oxide can influence vasodilation or vasoconstriction when insufficient is of interest. The ability of nitric oxide to reverse polarity of signaling

molecules could function to increase or decrease the flow of energy producing or energy metabolizing molecules in the sympathetic and parasympathetic nervous system has a homeostatic value. Vasoconstriction could create similar problems to those encountered in adrenal fatigue syndrome. The flow and transport of molecules in the bloodstream could be restricted by vasoconstriction. This could also explain why energy rich foods such as complex carbs, sugars and coffee to name a few are craved. It could also explain why the vascular systems in obese individuals is constricted. Since the flow of energy is restricted through vasoconstriction, the body may seek quick energy sources or energy rich foods to supplement the reduced flow of energy in the blood. Addiction could stem from a disease in the vascular system resulting in a constricted vascular system due to an estrogen deficiency, diminished nitric oxide expression, damage to the endothelium, and/or receptor desensitization. This relationship is of interest and will need to be researched further.

Bibliography

1. Bagatell CJ., *et al*. "Effects of endogenous testosterone and estradiol on sexual behavior in normal young men". *The Journal of Clinical Endocrinology and Metabolism* 78.3 (1994): 711-716.
2. Freeman EW., *et al*. "Symptoms in the Menopausal Transition". *Obstetrics and Gynecology* 111.1 (2008): 127-136.
3. Davison SL and Davis SR. "Androgenic hormones and aging - The link with female sexual function". *Hormones and Behavior* 59.5 (2011): 745-753.
4. Farhund DD., *et al*. "Happiness and Health: The Biological Factors- Systematic Review Article". *Iranian Journal of Public Health* 43.11 (2014): 1468-1477.
5. K Hishikawa., *et al*. "Up-regulation of nitric oxide synthase by estradiol in human aorticendothelial cells". *FEBS Letters* 360.3 (1995): 291-293.
6. Friedl R., *et al*. "Testosterone inhibits expression of inducible nitric oxide synthase in murine macrophages". *Life Sciences* 68.4 (2000): 417-429.
7. Jung K., *et al*. "2-Arachidonoylglycerol Signaling in Forebrain Regulates Systemic Energy Metabolism". *Cell Metabolism* 15.3 (2012): 299-310.
8. Akcay F., *et al*. "Effect of breast-feeding on concentration of nitric oxide in breast milk". *Annals of Clinical Biochemistry* 39.1 (2002): 68-69.
9. S Zou., *et al*. "Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System". *International Journal of Molecular Sciences* 19.3 (2018): 833.
10. Gaitán A., *et al*. "Endocannabinoid Metabolome Characterization of Transitional and Mature Human Milk". *Nutrients* 10.9 (2018): E1294.

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