OKLAHOMA STATE UNIVERSITY
CENTER FOR HEALTH SCIENCES

BDNF levels affected by the synthetic cannabinoid WIN55,212-2 in adolescent rats.

Torres Alejandro G., Vazquez-Sanroman Dolores PhD.

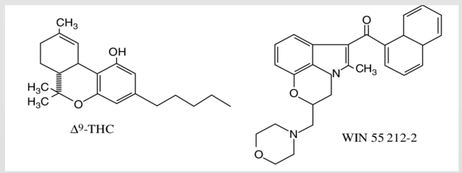
Department of Anatomy and Cell Biology , Oklahoma State University-Center for Health Sciences

INTRODUCTION

Cannabinoids are molecules that bind to endocannabinoid receptors CB1 and CB2 present in the central and peripheral nervous system[1].

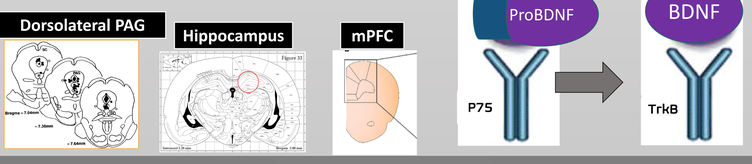
The synthetic CB1/CB2 receptor agonist WIN55,212-2 (WIN) emulates the effects of delta-9-tetrahydrocannabinol (THC), the psychoactive component of cannabis plant[2].

Interestingly, endocannabinoids and neurotrophins, play critical roles in mood, immune and endocrine homeostasis, stress/anxiety response, and neuroplasticity. Endocannabinoids (eCBs) and neurotrophins, particularly brain derived neurotrophic factor (BDNF), are potent neuromodulators that play critical roles in many behavioral and physiological processes[1]. Disruption of either BDNF or endocannabinoid signaling is associated with an overlapping set of neurologic and psychiatric diseases[3]. Recent studies support the interaction between BDNF and endocannabinoid signaling to control neurogenesis.[4] The chronic use of synthetic cannabinoids during adolescence, a vulnerable stage for brain development may affect or alter the homeostasis and neuroplasticity dependent on BDNF.



The hippocampus is a brain structure that is deeply involved in memory formation and retrieval. Animal studies, suggest that acute cannabis administration disrupts the hippocampal-dependent spatial learning in rats[5]. The periaqueductal gray (PAG) contributes to the modulation of anxiety, fear, and nociception (all of which may produce physical discomfort) linked with chronic exposure opioid abuse[6,7].

BDNF is found in two isoforms; the precursor proBDNF and matureBDNF bind to specific receptors, resulting in different functional outcomes. proBDNF binds P75r activating cell signaling associated with dendritic pruning or apoptosis [8]. However, the effects of exogenous or synthetic cannabinoids in proBDNF or matureBDNF in the adolescent brain remain unknown.



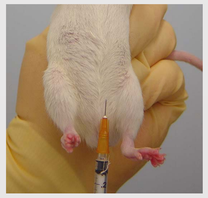
SPECIFIC AIMS

To determine the effect of chronic exposure to WIN 55,212-2 on pro and mature BDNF levels in PFC, Hippocampus, PAG ,and peripheral serum concentrations in the adolescent rat.

HYPOTHESIS

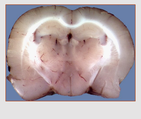
Chronic exposure to WIN will affect the baseline levels of mature and proBDNF expressed in the brain and the periphery of adolescent rats. This could support the synergistic interaction of BDNF and cannabinoids to promote neuroplasticity.

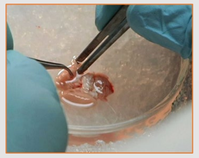
METHODS

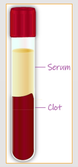


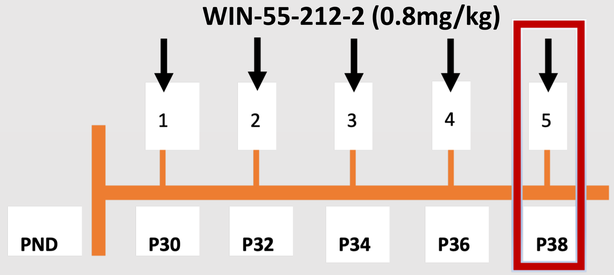
1. Male Sprague Dawley adolescent rats received five intraperitoneal (IP) injections of either vehicle (1 mL/kg i.p.) or the cannabinoid (CB1 and CB2 receptor) agonist WIN-55-212-2 (0.8 mg/kg i.p.) twice daily every **48 hours**.

2.PFC,HIP, and PAG was dissected, also truncal blood samples were collected to analyze BDNF content in brain tissue and serum.



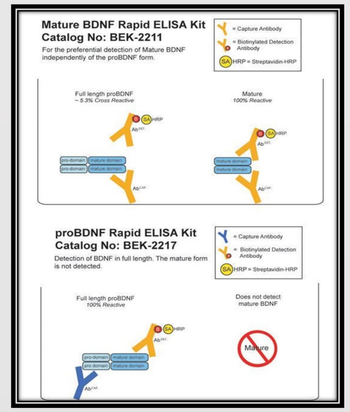






3.Brain tissue was homogenized using ultrasonication. Truncal blood and homogenates were centrifuged for 20 minutes at 14,000rpm and kept on ice.

4.Brain homogenates and serum were processed by ELISA immunoassay to determine the concentrations for pro and matureBDNF (Biosensis-mature and proBDNF/Rapid ELISA BEK-2211,2217).



RESULTS

BDNF PAG Levels

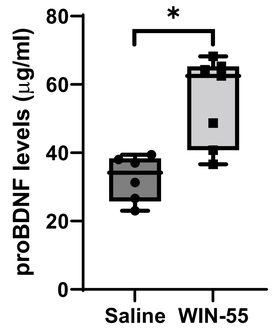


Figure 1: One-way ANOVA showed significant differences for treatment **{F 1,11= 12.57, p<0.05}** Post hoc comparisons demonstrated that WIN increased proBDNF levels in the dorsolateral PAG.

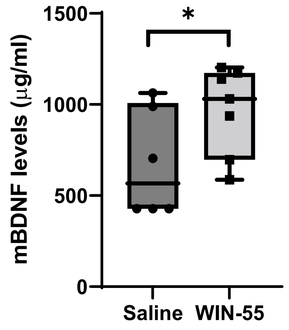


Figure 2: One way ANOVA showed significant differences for treatment **{F 1,11= 2.63, p<0.05}** Post hoc comparisons demonstrated that WIN boosted matureBDNF levels in the dorsolateral PAG.

mBDNF Hippocampus Levels

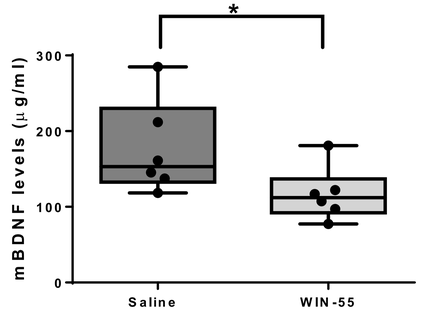


Figure 5: One-way ANOVA showed significant differences for treatment **{F 1,11=4.97, p<0.05}** Post hoc comparisons demonstrated that WIN increased matureBDNF levels in the hippocampus.

BDNF Serum Levels

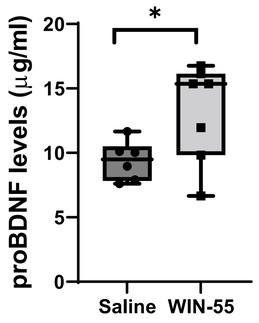


Figure 3: One-way ANOVA showed significant differences for treatment **{F 1,11= 5.15, p<0.05}** Post hoc comparisons demonstrated that WIN boosted proBDNF levels in the periphery.

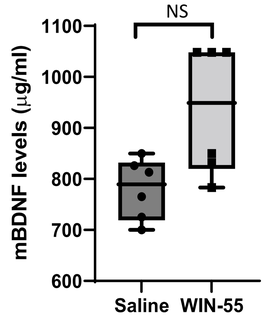


Figure 4: One-way ANOVA failed to show significant differences **{F 1,11= 0.56, p.0.09}**, although this data suggest an increased trend line on matureBDNF levels in the periphery.

mBDNF PFC Levels

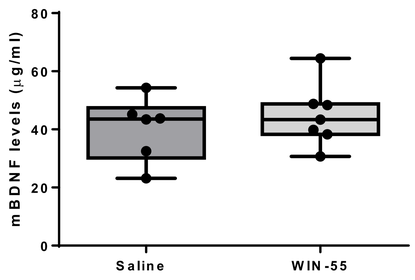


Figure 6: One-way ANOVA failed to show significant differences for treatment in PFC **{F 1,11= 0.54, p.0.47}**WIN did not cause a change in mBDNF in the medial PFC.

DISCUSSION

The chronic exposure of the synthetic cannabinoid WIN55,212-2during adolescence modifies the proBDNF/mBDNF ratio in the dorsal PAG and periphery, also increasing mBDNF levels in the hippocampus suggesting that proBDNF/mBDNF ratio are involved in endocannabinoid-mediated adolescence brain plasticity.

FUTURE DIRECTIONS

- ❑ Measure the proBDNF levels from PFC, hippocampus , and cerebellum from WIN treated animals.
- ❑ Investigate the effects of self administration of THC on BDNF expression in brain areas involved in reward and motivation, using a BDNF mutant (val66met) mice model.
- ❑ Study how the microbiome gut-brain axis is affected due to ingestion/administration of cannabis-derived products.

REFERENCES

1. Ferreira, F. F., Ribeiro, F. F., Rodrigues, R. S., Sebastião, A. M., & Xapelli, S. (2018). Brain-derived neurotrophic factor (BDNF) role in cannabinoid-mediated neurogenesis. Frontiers in Cellular Neuroscience, 12. https://doi.org/10.3389/fncel.2018.00441
2. Kirschmann, E. K., McCalley, D. M., Edwards, C. M., & Torregrossa, M. M. (2017). Consequences of adolescent exposure to the cannabinoid receptor agonist WIN55,212-2 on working memory in female rats. Frontiers in Behavioral Neuroscience, 11. https://doi.org/10.3389/fnbeh.2017.00137
3. Ibarra-Lecue, I., Pilar-Cuéllar, F., Muguruza, C., Florensa-Zanuy, E., Díaz, Á., Urigüen, L., Castro, E., Pazos, A., & Callado, L. F. (2018). The endocannabinoid system in mental disorders: Evidence from human brain studies. Biochemical Pharmacology, 157, 97–107. https://doi.org/10.1016/j.bcp.2018.07.009
4. Ferreira, F. F., Ribeiro, F. F., Rodrigues, R. S., Sebastião, A. M., & Xapelli, S. (2018). Brain-derived neurotrophic factor (BDNF) role in cannabinoid-mediated neurogenesis. Frontiers in Cellular Neuroscience, 12. https://doi.org/10.3389/fncel.2018.00441
5. Kutlu, M. G., & Gould, T. J. (2016). Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learning & memory (Cold Spring Harbor, N.Y.), 23(10), 515–533
6. Gobira, P. H., Almeida-Santos, A. F., Guimaraes, F. S., Moreira, F. A., & Aguiar, D. C. (2016). Role of the endocannabinoid 2-arachidonoylglycerol in aversive responses mediated by the dorsolateral Periaqueductal Grey. European Neuropsychopharmacology, 26(1), 15–22. https://doi.org/10.1016/j.euroneuro.2015.11.014
7. Yin, J.-B., Wu, H.-H., Dong, Y.-L., Zhang, T., Wang, J., Zhang, Y., Wei, Y.-Y., Lu, Y.-C., Wu, S.-X., Wang, W., & Li, Y.-Q. (2014). Neurochemical properties of BDNF-containing neurons projecting to rostral ventromedial medulla in the ventrolateral periaqueductal gray. Frontiers in Neural Circuits, 8. https://doi.org/10.3389/fncir.2014.00137
8. Sandhya, V. K., Raju, R., Verma, R., Advani, J., Sharma, R., Radhakrishnan, A., Nanjappa, V., Narayana, J., Somani, B. L., Mukherjee, K. K., Pandey, A., Christopher, R., & Prasad, T. S. (2013). A network map of BDNF/TRKB and BDNF/p75NTR signaling system. Journal of Cell Communication and Signaling, 7(4), 301–307. https://doi.org/10.1007/s12079-013-0200-z

ACKNOWLEDGMENTS

Oklahoma State University-Intramural OVPR 2021-2022 , Oklahoma State University-Start up Funds(Vazquez-Sanroman) and OSU-CHS Animal Care facilities - Ivy Cooper .