The synthetic cannabinoid, WIN-55212-2, leads to changes of proBDNF/BDNF ratio levels in the PAG and blood concentrations in the adolescent rat.

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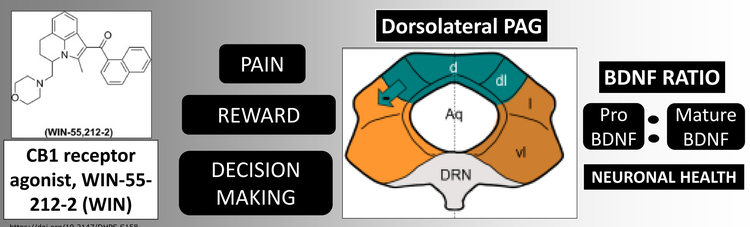
INTRODUCTION

Marijuana, a psychoactive drug that activates cannabinoid-1 (CB1) receptors in the brain, is the most prevalently abused illicit drug among American adolescents and young adults (1). Cannabis and, to a lesser extent, synthetic cannabinoids as CB1 receptor agonist, WIN-55-212-2 (WIN) analog to Δ-9-THC, when administered to rats and mice during adolescence, leads to long-lasting deficits. Also, chronic administrations of WIN-55 during adolescence have been associated with various neural and behavioral abnormalities, some of which may persist until adulthood (4). Moreover, this vulnerability might involve brain areas densely packed with CB1 receptors and linked to decision making and reward processing such as the nucleus accumbens, ventral tegmental area, and the periaqueductal gray area (PAG). The PAG is a structure that has been long-known to play an essential role in endogenous analgesia, vocalizations, defensive behaviors, and autonomic regulation (2). In addition, evidence suggests the PAG is also situated to mediate complex emotional and motivated behaviors through its vast connections throughout the brain (3). Endocannabinoids and neurotrophins, particularly brain-derived neurotrophic factors (BDNF), are potent neuromodulators that play critical roles in decision making, reward processing, and motivation. For example, BDNF within the mesocorticolimbic dopamine system is a positive modulator of psychostimulant and opiate reward, and recent evidence suggests that BDNF released from projection neurons in the PAG might participate in pain modulation in adult rats (2). Moreover, neurons within the PAG are a release-site for BDNF after opioid administration. However, while evidence suggests that BDNF might participate in dopamine and endocannabinoid-mediated drug reward response, the role of this neurotrophin during development and in the presence of synthetic cannabinoids is still unknown. BDNF has well-established pro-survival effects, whereas its precursor protein, proBDNF, induces apoptosis. Thus, it has been suggested that the proBDNF/BDNF ratio could indicate neuronal health (5); however, the roles of the mBDNF/proBDNF after synthetic cannabinoids during this critical period is not clearly understood. Therefore, the present study aimed to evaluate the effect of adolescent exposure to WIN on the proBDNF/BDNF ratio levels in the PAG and blood concentrations in the adolescent rat.



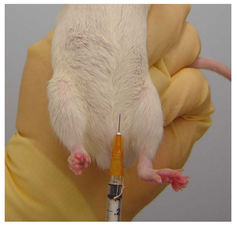
OBJECTIVES

Determine proBDNF and mBDNF levels of expression in the PAG and serum of WIN 55212-2 treated rats.

METHODS

Brain Processing and ELISA assay

- ✓ Adolescent rats received five daily intraperitoneal (IP) injections of either vehicle (1 mL/kg i.p.) or the cannabinoid (CB1 and CB2 receptor) agonist WIN-55-212-2 (0.2 mg/kg i.p. every other day).
- ✓ The PAG was dissected, and truncal blood samples were collected to analyze.
- ✓ Brain tissue and serum were used in an ELISA immunoassay to determine the concentrations for pro and matureBDNF.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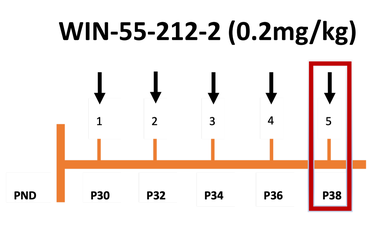

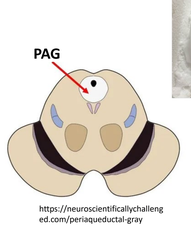

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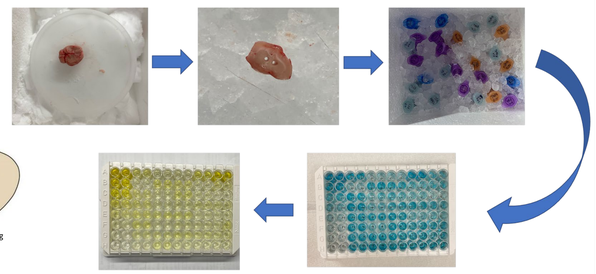

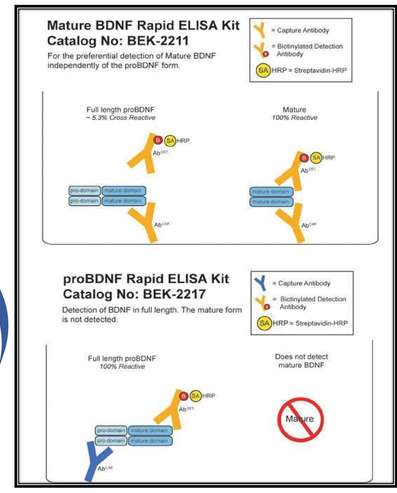

RESULTS

BDNF Brain Levels

Periaqueductal Gray Area

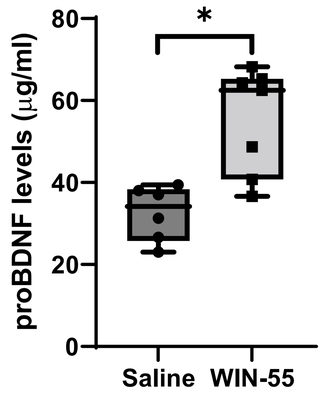

Figure 1: One way ANOVA showed significant differences for treatment {F 1,11= 12.57, p<0.05} Post hoc comparisons demonstrated that CB1 synthetic agonist increased proBDNF levels in the dorsolateral PAG.

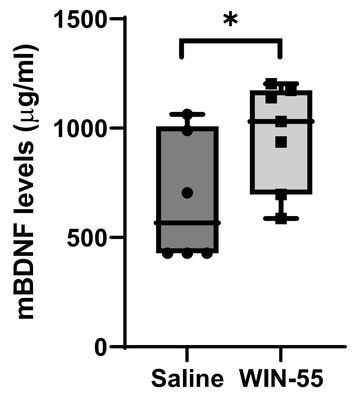

Figure 2: One way ANOVA showed significant differences for treatment {F 1,11= 2.63, p<0.05} Post hoc comparisons demonstrated that CB1 synthetic agonist boosted matureBDNF levels in the dorsolateral PAG.

BDNF Serum Levels

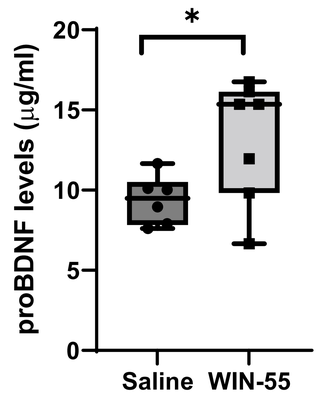

Figure 3: One way ANOVA showed significant differences for treatment {F 1,11= 5.15, p<0.05} Post hoc comparisons demonstrated that CB1 synthetic agonist boosted proBDNF levels in the periphery.

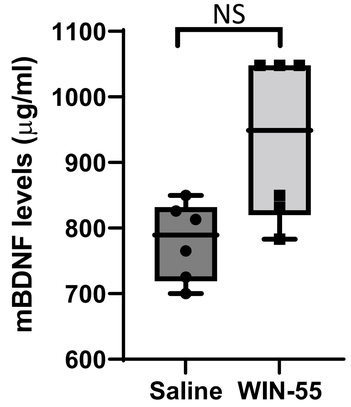

Figure 4: One way ANOVA failed to show significant differences {F 1,11= 0.56, p.0.09}, although this data suggest an increased trend line on matureBDNF levels in the periphery.

CONCLUSION

- Chronic exposure of the synthetic CB1 agonist modified the proBDNF/BDNF ratio drastically, increasing 33% proBDNF levels and 47% BDNF in the dorsal PAG; only proBDNF blood concentrations were significantly increased (47%) compared to drug-naïve rats.
- Our study revealed that synthetic CB1 receptors during adolescence significantly increased proBDNF levels in brain tissue and blood, demonstrating that the PAG and proBDNF/BDNF ratio are involved in endocannabinoid-mediated neurotransmission.

REFERENCES

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