

Received: 2012.07.10
Accepted: 2012.09.13
Published: 2013.01.07

Effects of glucagon-like peptide-1 receptor stimulation and blockade on food consumption and body weight in rats treated with a cannabinoid CB1 receptor agonist WIN 55,212-2

BCDEF Elżbieta Radziszewska
ACDEFG Ewa Bojanowska

Department of Behavioral Pathophysiology, Institute of General and Experimental Pathology, Medical University of Lodz, Lodz, Poland

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

Author's address: Ewa Bojanowska, e-mail: ewa.bojanowska@umed.lodz.pl

Source of support: This work was supported by the grant No. 0056/B/P01/2011/40 from the National Centre for Science, Poland

Background: Glucagon-like peptide-1 (GLP-1) and endocannabinoids are involved in appetite control. Recently we have demonstrated that cannabinoid (CB)1 receptor antagonist and GLP-1 receptor agonist synergistically suppress food intake in the rat. The aim of the present study was to determine the effects of GLP-1 receptor stimulation or blockade on feeding behavior in rats treated with WIN 55,212-2, a CB1 receptor agonist.

Material/Methods: Experiments were performed on adult male Wistar rats. In the first experiment the effects of increasing doses (0.5–4.0 mg/kg) of WIN 55,212-2 injected intraperitoneally on 24-hour food consumption were tested. In further experiments a GLP-1 receptor antagonist, exendin (9-39), and WIN 55,212-2 or a GLP-1 receptor agonist, exendin-4, and WIN 55,212-2 were injected intraperitoneally at subthreshold doses (that alone did not change food intake and body weight) to investigate whether these agents may interact to affect food intake in rats.

Results: WIN 55,212-2 administered at low doses (0.5–2 mg/kg) did not markedly change 24-hour food consumption; however, at the highest dose, daily food intake was inhibited. Combined administration of WIN 55,212-2 and exendin (9-39) did not change the amount of food consumed compared to either the control group or to each agent injected alone. Combined injection of WIN 55,212-2 and exendin-4 at subthreshold doses resulted in a significant decrease in food intake and body weight in rats.

Conclusions: Stimulation of the peripheral CB1 receptor by its agonist WIN 55,212-2 can induce anorexigenic effects or potentiate, even at a subthreshold dose, the effects of exendin-4, a known anorectic agent. Hence, this dual action of the cannabinoid system should be considered in the medical use of CB1 agonists.

key words: **GLP-1** **WIN 55,212-2** **exendin-4 • exendin (9-39)** **food intake**

full-text PDF: **ICID 883726** **PMID 23291632**  2504  —  3  38

Background

Cannabis plants have been used for medical purposes for many years, primarily as agents for alleviating pain and enhancing appetite [1,2]. However, due to the high psychoactivity of compounds found in marijuana, cannabis plants have generally not been considered as therapeutic agents in conventional medicine [1]. This changed when Δ^9 tetrahydrocannabinol (THC) was identified as the main constituent of marijuana producing appetite stimulation and when the role of the endocannabinoid system in the regulation of the body energy homeostasis was discovered [2]. Anandamide and 2-arachidonylglycerol are the main components of this system [3]. Endocannabinoids modulate food intake through the cannabinoid (CB)1 receptor [4], located in the hypothalamic neurons involved in food intake control as well as in vagal afferent neurons in the gastrointestinal tract [5]. Anandamide injected both peripherally and centrally at low doses has been shown to increase food intake [2]. Similar effects are evoked by 2-arachidonylglycerol [1]. On the other hand, appetite-stimulating THC activity was confirmed in the treatment of anorexia accompanying Alzheimer's disease [1], senile dementia [1], anorexia nervosa [2], and acquired immunodeficiency syndrome [6].

However, comparison of the effects of different THC doses on food intake in various animal species has shown discrepant results [7]. Cannabinoids have been found to both stimulate and inhibit food intake. The decrease in food intake was observed after administration of high doses of THC and can be explained by the sedative actions of this agent. Similar observations have been made regarding the effect of another CB1 receptor agonist, WIN 55,212-2, on food consumption. Low doses (0.5–2 mg/kg) injected peripherally induced an increase in food consumption [8–11]. At the lowest dose (0.5 mg/kg) the tendency for abnormally large food intake was observed as soon as 1 hour after injection and persisted for up to 2 hours; whereas after a dose of 1 and 2 mg/kg, the tendency for hyperphagia was seen for up to 6 hours after administration [8]. It seems to be surprising that at high doses the effects of WIN 55,212-2 are opposite to those seen after low doses. High doses of WIN 55,212-2 result in a decrease in food intake and significant weight loss [8,12,13]. Similar anorectic effects were induced by another synthetic CB1 receptor agonist, HU210, also when administered at high doses [14].

It should be emphasized that in the studies published so far, the effects of WIN 55,212-2 on food consumption were investigated within the period of up to 6 hours after injection. However, considering the possible use of CB1 receptor agonists in the treatment of anorexia, it is important to investigate whether they can significantly affect energy balance for a period of time longer than a few hours after administration. Therefore, in this study we investigated the effects of

increasing doses of WIN 55,212-2 on 24-hour food intake and body weight changes.

Endocannabinoids were reported to modulate the effects of orexigenic and anorexigenic neurotransmitters [15] and hormones, such as GLP-1 [16], on food intake. GLP-1 is a neuropeptide secreted from intestinal L cells and neurons located in the nucleus of the solitary tract in the brainstem [17]. The GLP-1 receptor occurs centrally in the brain areas associated with energy balance regulation and peripherally in vagal afferents [18], which pass information from the alimentary tract to the feeding centers in the brain.

Stimulation of GLP-1 receptor induces suppression of appetite, inhibition of gastric emptying, and an increase in insulin secretion [19]. Exogenous GLP-1 analogues or GLP-1 receptor agonists, such as exenatide and liraglutide, were demonstrated to suppress appetite in rodents, humans and other primates [18]. On the other hand, pharmacological blockade of the central GLP-1 receptor by its antagonist, exendin (9-39), results in an increase in food intake and body weight in the rat [20,21].

Since GLP-1 and CB1 receptors are expressed on vagal afferent neurons in the gastrointestinal tract, it seems that the combined administration of agents changing the activity of both receptors could result in the reciprocal stimulation or inhibition of their effects on appetite. Recently, we demonstrated that blockade of the CB1 receptor by its antagonist, AM 251, and stimulation of the GLP-1 receptor by exendin-4 acts synergistically in terms of the reduction of food intake and body weight in rats [16]. Thus, with reference to the above-mentioned study, it would be useful to investigate whether a similar relationship would occur when the CB1 receptor is stimulated and the GLP-1 receptor is blocked. Therefore, the aim of this study was to determine if exendin (9-39), the GLP-1 receptor antagonist, and WIN 55,212-2, the CB1 receptor agonist, would potentiate their effects on appetite. Additionally, the effects of simultaneous stimulation of the GLP-1 receptor by exendin-4 and the CB1 receptor by WIN 55,212-2 on food consumption and body weight changes were tested.

Material and Methods

Animals

The study was carried out on male Wistar rats weighing 280 to 320 g. The animals were housed individually in plastic cages and maintained on a 12:12 light-dark cycle at 20°C to 22°C. The animals had free access to standard rat chow LSM (WkiMP "AGROPOL", Motycz, Poland) and water. Each rat received a preweighed amount of pelleted chow and tap water every day. Four days prior to injection, the rats were habituated to experimental

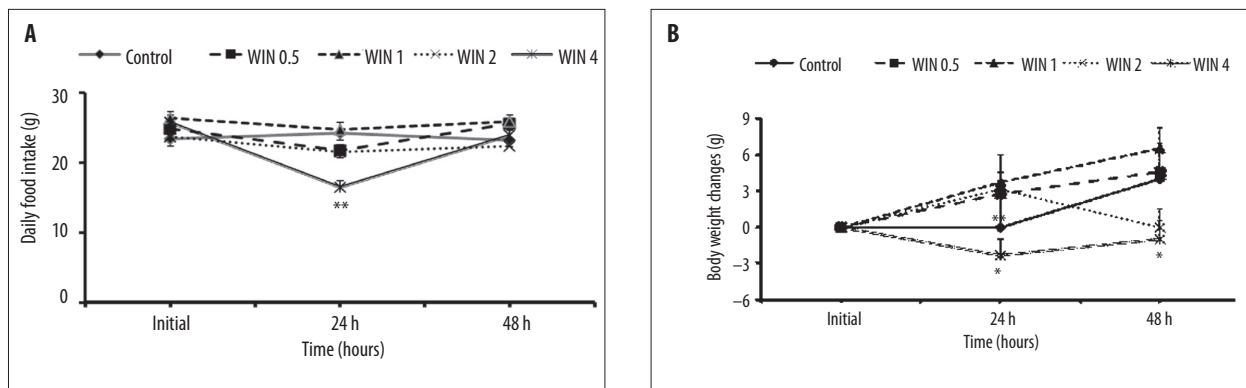


Figure 1. Effects of intraperitoneal administration of various doses (0.5, 1.0, 2.0, 4.0 mg/kg) of a cannabinoid CB1 receptor agonist, WIN 55,212-2 (WIN), on daily food intake (panel **A**) and body weight changes (panel **B**) in the rat. The initial values in panel **A** are the mean food consumption during two consecutive days before the injection of the drugs. The subsequent measurements were made 24 and 48 hours after injections. Body weight changes in all groups were measured on the day of injection and compared to results obtained 24 and 48 hours after the injection. Data are mean \pm SEM. * $p < 0.05$; ** $p < 0.001$.

conditions to reduce the possible effects of stress on results. Each group included 5 to 9 animals. All the procedures were approved by the Ethics Committee at the Medical University of Lodz.

Experimental procedures

The first experiment was aimed at determining the effects of increasing doses of WIN 55,212-2 on feeding behavior and finding the lowest dose that can significantly affect food intake. Rats were injected intraperitoneally with WIN 55,212-2 ((R)-(+)-[2,3-Dihydro-5-methyl-3[(4-naphthalenyl)methanone mesylate, SIGMA, St. Louis, MO, USA) at a dose of 0.5, 1.0, 2.0 and 4.0 mg/kg. Initially WIN 55,212-2 was dissolved in DMSO (dimethyl sulfoxide, SIGMA, St. Louis, MO, USA) and then diluted with 0.9% NaCl using Cremophor TWEEN 80 (SIGMA, St. Louis, MO, USA), 2%: 97%: 1% v/v, respectively, until obtaining the required concentration. Food intake and body weight were recorded every 24 hours 2 days prior to and 2 days after the injection.

The aim of the second experiment was to investigate whether WIN 55,212-2 and exendin (9-39) (BACHEM, Switzerland) at subthreshold doses showed synergistic effects on food intake or body weight gain. The rats were administered exendin (9-39) and WIN 55,212-2 alone or in combination at doses of 160 μ g/kg and 1 mg/kg, respectively; 0.9% NaCl was used in the control group. Exendin (9-39) was dissolved in sterile 0.9% NaCl. WIN 55,212-2 was administered 15 minutes after exendin (9-39). Daily food intake and body weight were recorded as in the previous experiment.

The aim of the third experiment was to investigate whether exendin-4 (BACHEM, Switzerland) and WIN 55,212-2 would reciprocally modify their effects on food intake. The rats were injected intraperitoneally with each agent either separately or

in combination at a dose of 3 μ g/kg and 2 mg/kg, respectively. Control rats received 0.9% NaCl. Exendin-4 was dissolved in sterile 0.9% NaCl. WIN 55,212-2 was injected 15 minutes after exendin-4 injection. Daily food intake and body weight were recorded as indicated above.

Statistical analysis

The results of the experiments were analysed with statistical software STATISTICA 8 (StatSoft, Poland) with the use of repeated-measures analysis of variance (ANOVA) and post-hoc analysis (Fisher's NIR test). A p -value < 0.05 was set to be statistically significant.

Results

There were no significant differences in initial body weight or in the amount of food consumed by the rats among all the experimental groups. WIN 55,212-2 did not significantly change the 24-hour food intake or body weight when administered at low doses (0.5, 1.0 and 2.0 mg/kg). However, when the drug was administered at the highest dose (4.0 mg/kg) it resulted in a marked ($p < 0.001$) decrease in the amount of food consumed at 24 hours, but not at 48 hours, after the injection. Also, body weight was decreased, and this effect was significant at 24 and 48 hours after the injection ($p < 0.05$, Figure 1).

Exendin (9-39) and WIN 55,212-2 each administered alone did not change daily food intake or body weight as compared with control animals. Combined administration of these agents did not significantly affect these parameters (Figure 2).

Exendin-4 and WIN 55,212-2 injected alone did not cause statistically significant differences in daily food intake or body

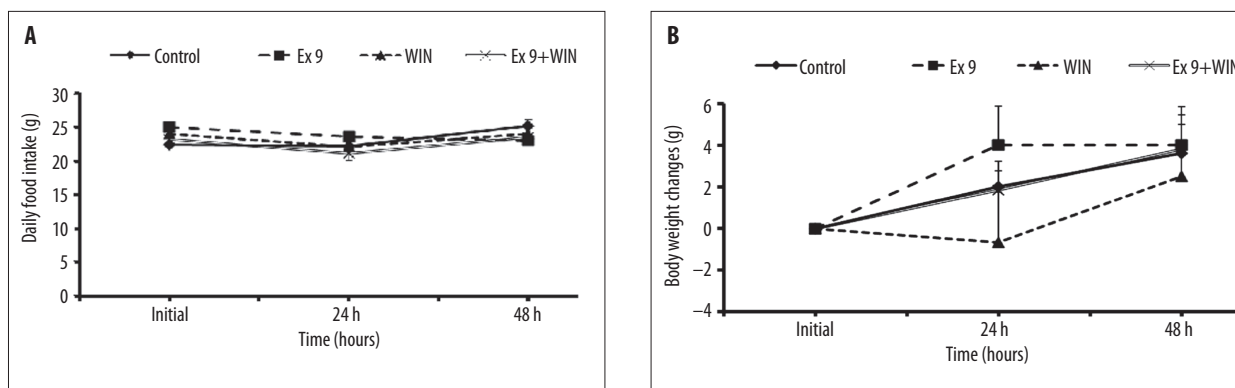


Figure 2. Effects of intraperitoneal administration of a combination of a GLP-1 receptor antagonist exendin (9-39) (Ex 9) and a cannabinoid CB1 receptor agonist WIN 55,212-2 (WIN) on daily food intake (panel **A**) and body weight changes (panel **B**) in the rat. The initial values in panel **A** are the mean food consumption during two consecutive days before the injection of the drug. The subsequent measurements were made 24 and 48 hours after injections. Body weight in all groups was measured on the day of injection and compared to results obtained 24 and 48 hours after the injection. There were no significant differences. Data are mean \pm SEM.

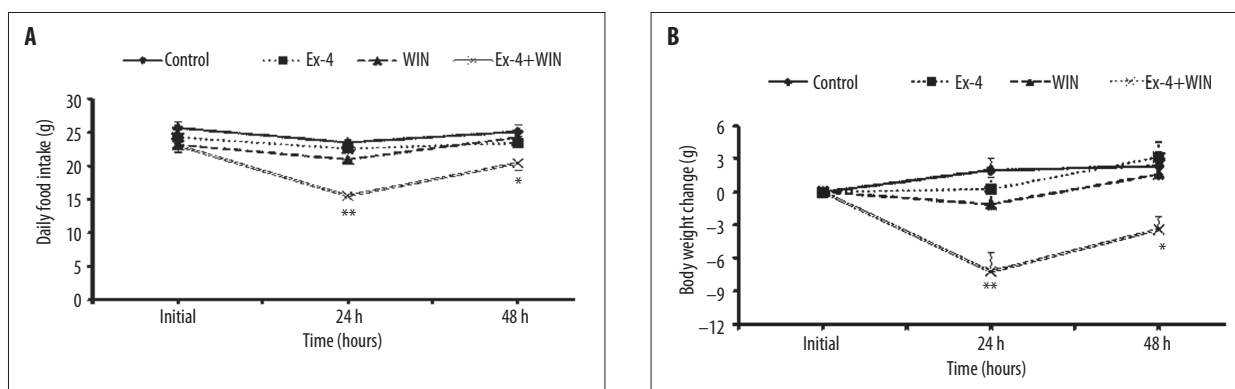


Figure 3. Effects of intraperitoneal administration of a combination of a GLP-1 receptor agonist, exendin-4 (Ex 4), and a cannabinoid CB1 receptor agonist, WIN 55,212-2 (WIN), on daily food intake (panel **A**) and body weight changes (panel **B**) in the rat. The initial values in panel **A** are the mean food consumption during two consecutive days before the injection of the drug. The subsequent measurements were made 24 and 48 hours after injections. Body weight in all groups was measured on the day of injection and compared to results obtained 24 and 48 hours after the injection. Data are mean \pm SEM. * $p < 0.01$; ** $p < 0.001$.

weight compared to the control animals. However, a combination of these agents induced a decrease in food intake on the first and second day after the injection ($p < 0.001$ and $p < 0.01$, respectively). Also, a significant body weight loss was observed on the first day ($p < 0.001$) and maintained on the second day after injection ($p < 0.01$, Figure 3).

Discussion

We found that WIN 55,212-2, a synthetic CB1 receptor agonist, injected at doses of 0.5 to 2.0 mg/kg did not have any significant effects on 24-hour food intake, whereas a dose of 4 mg/kg inhibited food intake and subsequently resulted in body weight loss. We also found that the inhibitory effects of

a single dose of WIN 55,212-2 was temporary and lasted only 24 hours. Interestingly, this decrease in food intake was accompanied by body weight loss, which was maintained longer than the anorexigenic effect. These findings may indicate that a high dose of WIN 55,212-2 causes a negative energy balance, not only due to an anorexigenic effect, but also likely due to increased energy expenditure. If this is the case, it would mean that the CB1 receptor agonist applied at high doses causes effects characteristic of CB1 receptor antagonists [22,23].

Earlier studies have demonstrated divergent effects of WIN 55,212-2 on food consumption. The stimulatory effects of low doses of WIN 55,212-2 injected peripherally has often been described [8–11]. However, the orexigenic effects of this drug

often lasted only for a few hours after drug administration [8]. This fact explains why we did not observe any marked changes in food consumption in rats treated with similar doses of WIN 55,212-2 at 24 hours after the injection. On the other hand, WIN 55,212-2 used at a dose comparable to or higher than the highest dose administered in our study, suppressed appetite [8]. Similarly, AM 404, a drug enhancing the action of endocannabinoids by blocking anandamide reuptake, demonstrated an inhibitory effect on food intake [24]. It seems that overstimulation of the CB1 receptor with high doses of the above-mentioned agonists can lead to its desensitization. This, in turn, may result in reduced activity of the CB1 receptor and, consequently, in the loss of its ability to respond to stimulation by endogenous agents under physiological conditions [25]. As WIN 55,212-2 is a synthetic CB1 receptor agonist, it demonstrates higher durability and capability of binding with CB1 receptors compared with natural neuromediators [26]. Therefore, when administered at high ("pharmacologic") doses, it can act as a cannabinoid antagonist [27]. This fact could explain the paradoxical decrease in appetite observed after administration of CB1 receptor agonists in this and other research studies.

Different effects of high and low doses of cannabinoids on appetite can also result from their influence on various neurotransmitters mediating the action of cannabinoids in the brain. Low doses of cannabinoids were demonstrated to inhibit glutamate release and produce hyperphagia, whereas high doses inhibit the secretion of gamma-aminoacetic acid and cause hypophagia [28]. The fact that higher doses of cannabinoids inhibit appetite can be additionally explained by their suppressive effects on gastrointestinal motility [29] and gastric emptying [12].

In the second experiment we investigated whether a GLP-1 receptor antagonist and a CB1 receptor agonist can reciprocally modify their effects on food intake. Earlier reports published by other authors indicate that intracerebroventricular administration of exendin (9-39) stimulates food intake [21,30]. Moreover, exendin (9-39) was found to enhance the orexigenic action of neuropeptide Y [21] and attenuate the anorexigenic effect of lipopolysaccharide [31], thus indicating that it may modify the effects produced by other factors influencing appetite. On the other hand, previous studies demonstrated that co-expression of CB1 and orexin 1 receptors enhances the activity of the latter receptor [32]. Because CB1 [33] and GLP-1 [34] receptors were detected in vagal afferent neurons transferring information from the gastrointestinal tract to the brain feeding centers, it may be assumed that endocannabinoids and GLP-1 would cooperate in the modification of these centers' activity. We found, however, that simultaneous peripheral administration of WIN 55,212-2 and exendin (9-39) did not significantly change appetite or body weight of rats. Hence, under conditions of our experiment, exendin (9-39), a GLP-1 receptor antagonist together with WIN 55,212-2, a CB1 receptor agonist, did not evoke a synergistic stimulatory effect on

appetite or body weight gain. This is in agreement with our earlier observation that exendin (9-39) does not modify the anorexigenic effect of AM 251, a CB1 receptor antagonist [16].

In our third experiment we demonstrated that WIN 55,212-2 and exendin-4 each injected alone at low doses did not significantly affect food intake or body weight in rats, whereas their combined administration at subthreshold doses caused a decrease in food consumption and in body weight. It is of interest that this effect is similar to that described in our previous study, where exendin-4 and AM 251, a CB1 receptor antagonist, showed a synergistic effect on the reduction of food intake and body weight [16]. The above results demonstrate that the anorexigenic effect of exendin-4 may be enhanced under both the blockade and stimulation of CB1 receptor. However, it seems that the unexpected enhancement of anorexigenic effects of exendin-4 by WIN 55,212-2 does not result from its direct influence on feeding centers in the brain, but rather from other mechanisms indirectly suppressing appetite.

The decrease in food consumption in animals treated with both exendin-4 and WIN 55,212-2 could be the result of their additive, inhibitory effects on gastric emptying [35, 36]. Another possible mechanism by which both agents decreased food consumption is their suppressive effect on locomotor activity. Earlier studies demonstrated that both WIN 55,212-2 and exendin-4 at the doses similar to those used in our study decreased motor activity in animals [37,38]. Thus, the sedative action of both drugs can be responsible for the decrease in appetite.

Conclusions

The results of our study indicate that WIN 55,212-2, a CB1 receptor agonist, injected intraperitoneally at low doses does not significantly alter daily food consumption. These results also confirm earlier reports that the CB1 receptor agonist injected at a high dose inhibits food intake. Furthermore, we have demonstrated that simultaneous administration of 2 potentially orexigenic agents, exendin (9-39) and WIN 55,212-2, does not modify food intake in rats. However, the anorexigenic actions of exendin-4, a GLP-1 receptor agonist, are enhanced by even a subthreshold dose of WIN 55,212-2. Thus, we conclude that, regarding the ambiguous role of peripheral CB1 receptors in the regulation of food intake, agonists of this receptor administered to induce appetite should be used with caution. Further studies are needed to explain the dual action of the cannabinoid system on feeding centers in the brain.

Acknowledgements

The authors wish to thank the experts of BioMed Proofreading for their excellent assistance with editing our article and for language revision.

References:

1. Pacher P, Bátkai S, Kunos G: The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev*, 2006; 58: 389–62
2. Kirkham TC: Cannabinoids and appetite: food craving and food pleasure. *Int Rev Psychiatry*, 2009; 21: 163–71
3. Richard D, Guesdon B, Timofeeva E: The brain endocannabinoid system in the regulation of energy balance. *Best Pract Res Clin Endocrinol Metab*, 2009; 23: 17–32
4. Trillou I, Delgorge C, Menet C, Arnone M, Soubrie P: CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int J Obesity*, 2004; 28: 640–48
5. Matias I, Di Marzo V: Endocannabinoids and the control of energy balance. *Trends Endocrinol Metab*, 2006; 18: 26–37
6. Haney M, Gunderson EW, Rabkin J et al: Dronabinol and marijuana in HIV-positive marijuana smokers. Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr*, 2007; 45: 545–54
7. Pagotto U, Marsicano G, Cota D et al: The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr Rev*, 2006; 27: 73–100
8. Merroun I, Errami M, Hoddah H: Influence of intracerebroventricular or intraperitoneal administration of cannabinoid receptor agonist (WIN 55,212-2) and inverse agonist (AM 251) on the regulation of food intake and hypothalamic serotonin levels. *Br J Nutr*, 2009; 101: 1569–78
9. Scopinho AA, Guimarães FS, Corrêa FM, Resstel LB: Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists. *Pharmacol Biochem Behav*, 2011; 98: 268–72
10. Ho J, Cox JM, Wagner EJ: Cannabinoid-induced hyperphagia: correlation with inhibition of proopiomelanocortin neurons? *Physiol Behav*, 2007; 92: 507–19
11. Gomez R, Navarro M, Ferrer B et al: A peripheral mechanism for CB1 cannabinoid receptor-dependent modulation of feeding. *J Neurosci*, 2002; 22: 9612–17
12. Abalo R, Cabezas PA, Lopez-Miranda V et al: Selective lack of tolerance to delayed gastric emptying after daily administration of WIN 55,212-2 in the rat. *Neurogastroenterol Motil*, 2009; 21: 1002–80
13. Aceto MD, Scates SM, Martin BB: Spontaneous and precipitated withdrawal with a synthetic cannabinoid, WIN 55212-2. *Eur J Pharmacol*, 2001; 75–81
14. Giuliani D, Ottani A, Ferrari F: Effects of the cannabinoid receptor agonist, HU 210, on ingestive behaviour and body weight of rats. *Eur J Pharmacol*, 2000; 275–79
15. Fride E, Bregman T, Kirkham TC: Endocannabinoids and food intake: Newborn suckling and appetite regulation. *Exp Biol Med*, 2005; 230: 225–34
16. Bojanowska E, Radziszewska E: Combined stimulation of GLP-1 receptor and inhibition of cannabinoid CB1 receptor act synergistically to reduce daily food intake and body weight in the rat. *J Physiol Pharmacol*, 2011; 62: 395–402
17. Bojanowska E: Physiology and pathophysiology of glucagon-like peptide-1 (GLP-1): the role of GLP-1 in the pathogenesis of diabetes mellitus, obesity, and stress. *Med Sci Monit*, 2005; 11: 271–78
18. Hayes MR, De Jonghe BC, Kanoski SE: Role of the glucagon-like peptide-1 receptor in the control of energy balance. *Physiol Behav*, 2010; 5: 503–10
19. Mudaliar S, Henry RR: Incretin therapies: Effects beyond glycemic control. *Am J Med*, 2009; 122: 25–36
20. Schick RR, Zimmermann JP, vorm Walde T, Schusdziarra V: Peptides that regulate food intake: glucagon-like peptide 1-(7-36) amide acts at lateral and medial hypothalamic sites to suppress feeding in rats. *Am J Physiol*, 2003; 284: R1427–35
21. Meeran K, O'Shea D, Edwards CM et al: Repeated intracerebroventricular administration of glucagon-like peptide-1-(7-36) amide or exendin-(9-39) alters body weight in the rat. *Endocrinology*, 1999; 140: 244–50
22. Addy C, Wright H, Van Laere K et al: The acyclic cb1r inverse agonist taranabant mediates weight loss by increasing energy expenditure and decreasing caloric intake. *Cell Metab*, 2008; 7: 68–78
23. Bajzer M, Olivier M, Haas MK et al: Cannabinoid receptor 1 (CB1) antagonism enhances glucose utilisation and activates brown adipose tissue in diet-induced obese mice. *Diabetologia*, 2011; 54: 3121–31
24. Reyes-Cabello C, Alen F, Gómez R et al: Effects of the anandamide uptake blocker AM404 on food intake depend on feeding status and route of administration. *Pharmacol Biochem Behav*, 2012; 101: 1–7
25. Martini L, Waldhoer M, Pusch M et al: Ligand-induced down-regulation of the cannabinoid 1 receptor is mediated by the G-protein-coupled receptor-associated sorting protein GASP1. *FASEB J*, 2007; 21: 802–11
26. Barna I, Till I, Haller J: Blood, adipose tissue and brain levels of the cannabinoid ligands WIN-55,212 and SR-141716A after their intraperitoneal injection in mice: Compound-specific and area-specific distribution within the brain. *Eur Neuropsychopharmacol*, 2009; 19: 533–41
27. Oka S, Wakui J, Gokoh M et al: Suppression by WIN55212-2, a cannabinoid receptor agonist, of inflammatory reactions in mouse ear: Interference with the actions of an endogenous ligand, 2-arachidonoylglycerol. *Eur J Pharmacol*, 2006; 154–62
28. Bellocchio L, Lafenêtre P, Cannich A et al: Bimodal control of stimulated food intake by the endocannabinoid system. *Nat Neurosci*, 2010; 13: 281–83
29. Abalo R, Vera G, López-Pérez AE et al: The gastrointestinal pharmacology of cannabinoids: Focus on motility. *Pharmacology*, 2012; 90: 1–10
30. Barrera JG, Jones KR, Herman JP et al: Hyperphagia and increased fat accumulation in two models of chronic CNS glucagon-like peptide-1 loss of function. *J Neurosci*, 2011; 31: 3904–13
31. Grill HJ, Carmody JS, Sadacca LA et al: Attenuation of lipopolysaccharide anorexia by antagonism of caudal brain stem but not forebrain GLP-1-R. *Am J Physiol*, 2004; 287: R1190–93
32. Hilairet S, Bouaboula M, Carrière D et al: Hypersensitization of the orexin 1 receptor. *J Biol Chem*, 2003; 278: 23731–37
33. Burdys G, Varro A, Dimaline R et al: Expression of cannabinoid CB1 receptors by vagal afferent neurons: kinetics and role in influencing neurochemical phenotype. *Am J Physiol*, 2010; 299: 63–69
34. Nakagawa A, Satake H, Nakabayashi H: Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. *Auton Neurosci*, 2004; 110: 36–43
35. Abalo R, Cabezas PA, Vera G et al: Cannabinoid-induced delayed gastric emptying is selectively increased upon intermittent administration in the rat: role of CB1 receptors. *Neurogastroenterol Motil*, 2011; 23: 457–67
36. Horner KM, Byrne NM, Cleghorn GJ et al: The effects of weight loss strategies on gastric emptying and appetite control. *Obesity Rev*, 2011; 12: 935–51
37. Mack CM, Moore CX, Jodka CM et al: Antiobesity action of peripheral exenatide (exendin-4) in rodents: effects on food intake, body weight, metabolic status and side-effect measures. *Int J Obes*, 2006; 30: 1332–40
38. Polissidis A, Galanopoulos A, Naxakis G et al: The cannabinoid CB1 receptor biphasically modulates motor activity and regulates dopamine and glutamate release region dependently. *Int J Neuropsychopharmacol*, 2012; 6: 1–11