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Research Article

Strain Differences in Cannabinoid-Reinforced Lever Press Discrimination

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Abstract *Background.* The Lewis (LEW) and Fischer 344 (F344) rat strains have been typically used to study certain genetic influences on drug use. There are important differences between these strains in terms of the self-administration of several drugs and in several neurochemical messengers including the endocannabinoid system. *Purpose.* To investigate whether these two strains exhibit differences in the self-administration of the cannabinoid agonist WIN 55,512-2. *Results.* Stable WIN 55,512-2 self-administration behavior was not achieved by either strain, but both exhibited some degree of active/inactive lever discrimination, with LEW rats showing better performance in this index. Injection of the CB_1 receptor antagonist/inverse agonist AM251 decreased active lever pressing in F344 rats. During extinction, we observed a nonsignificant increase in lever pressing, which subsequently disappeared. *Conclusion.* Our results point to subtle genetic influences in the sensitivity to cannabinoid reward that may contribute to interindividual differences in marihuana use and abuse in humans.

Keywords Lewis rats; Fischer 344 rats; WIN 55,512-2; AM251; self-administration; strain differences; endocannabinoid system

1. Introduction

Vulnerability to addiction is influenced by both environmental and genetic factors. Indeed, some twin studies suggest that about 50% of this vulnerability is heritable [1]. The Lewis (LEW) and Fischer 344 (F344) inbred and histocompatible rat strains are a useful model to approach from an experimental point of view the contribution of genetic factors in drug abuse and addiction. LEW rats self-administer larger amounts of most drugs of abuse than F344 rats (see [2] for a review). There are well documented neurochemical differences between these strains that may be related to their differential sensitivity to the effects of drugs of abuse. For example, through a transcriptome analysis, we identified several genes that are differentially expressed in the nucleus accumbens (NAcc) and prefrontal cortex (PFc) of LEW and F344 rats. The genes induced in the LEW strain were associated with oxygen transport, neurotransmitter processing, and fatty acid metabolism, while those that were repressed were implicated in physiological functions such as drug and proton transport, oligodendrocyte survival, and lipid catabolism [3]. In a more target-specific study, we focused on several parameters of the endogenous opioid system in the encephalon, demonstrating that binding to μ-opioid receptors was weaker in LEW rats than in F344 rats. The functional activity of these receptors was comparable in both strains, with the exception of the cingulate cortex and NAcc core, where enhanced μ-opioid receptor activity was observed in LEW rats. Furthermore, the basal content of proenkephalin mRNA was lower in LEW versus F344 rats [4].

In light of these results, and given the close relationship between the cannabinoid and opioid systems, we analyzed the levels of endocannabinoid-related proteins in the hippocampus of LEW and F344 rats [5]. LEW rats exhibited weaker CB_1 expression but stronger CB_2 expression than F344 rats. Furthermore, the N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD)/fatty acid amino hydrolase (FAAH) ratio was higher in the stratum pyramidale of the CA3 hippocampal field of F344 compared to that in LEW rats. We then focused on the two areas belonging to the mesocorticolimbic system, namely the NAcc and the prefrontal cortex, finding interesting differences in cannabinoid receptor binding in the lateral globus pallidus (F344 $>$ LEW) and in the gene expression of several elements of the endocannabinoid system [6].

In order to have a functional correlate of the differences in gene expression observed, in this work we have studied WIN 55,512-2 (WIN) self-administration in both strains. Interestingly, although neither robust nor stable WIN self-administration was obtained under our experimental conditions, LEW rats showed greater discrimination of the active versus the nonactive operandum, indicating that these rats are more sensitive to the rewarding effects of the cannabinoid. However, CB_1 receptor blockade only

diminished cannabinoid-reinforced behavior in F344 rats, suggesting that receptors other than CB_1 may mediate cannabinoid reinforcer-sensitivity in LEW rats.

2. Experimental procedures

2.1. Animals

Male F344 and LEW rats were used ($n = 14$ for each strain) weighing 250–275 g at the beginning of the experiments. All animals were maintained at a constant temperature ($20 \pm 2\,^{\circ}C$) on a 12-hour light/dark cycle (lights on at 08:00 AM), with ad libitum access to food (standard commercial rodent diet A04/A03; Panlab, Barcelona, Spain) and tap water. All animals were maintained and handled according to European Union guidelines for the care of laboratory animals (Directive 2010/63/EU) and the "Principles of Laboratory Animal Care" were followed.

2.2. Cannabinoid compounds

The cannabinoid agonist WIN 55,512-2 (Tocris Bioscience, Bristol, UK) was dissolved in 0.3% Tween 80 (Sigma-Aldrich, MO, USA) and sterile saline (0.9% NaCl) and protected from the light. The CB_1 antagonist/inverse agonist AM251 (Tocris) was dissolved in a vehicle solution composed of Tween 80, dimethylsulfoxide, (Sigma), and sterile saline (1:1:8).

2.3. Surgery

Rats were anesthetized with ketamine (40 mg/kg) and diazepam (10 mg/kg), and an intravenous catheter (polyvinyl chloride tubing; 0.064 ID) was then surgically introduced into the right jugular vein, at the approximate level of the atrium, passed subcutaneously, and exited in the midscapular region. After surgery, all animals were housed individually and allowed to recover for seven days. The catheter was flushed daily with heparinized saline (0.2 mL of 100 IU) to ensure its patency and with gentamicin (0.10 mg/mL) to protect against infection. No catheter problems were observed in any of the rats used in the analyses.

2.4. Equipment

Six operant chambers (Med-Associates, VT, USA) were used in this study, with two levers placed 14 cm apart on the front wall of the chamber. Microliter injection pumps (Pump 11 Plus; Harvard Apparatus, MA, USA) were used to intravenously deliver WIN or the vehicle.

2.5. Experimental procedure

We used a modified version of the WIN self-administration procedure previously described by Fattore et al. [7]. Animals were maintained at 90–95% of their original body weight for the entire procedure. After a seven-day postsurgical recovery period, animals began the behavioral studies, which were divided into three phases: acquisition (sessions 1–8), maintenance (sessions 9–23), and extinction (sessions 24–28). A fixed ratio 1 schedule of reinforcement was applied throughout the experiment, such that whenever a rat pressed the active lever, a 100 μL injection was administered by the pump over 15 s. Acquisition sessions lasted one hour and during sessions 1 and 2, a food pellet was placed in the active lever to facilitate acquisition. Maintenance and extinction sessions lasted for two hours. Other than this difference in session duration, acquisition and maintenance sessions were identical. To test the effects of CB_1 receptor blockade on WIN self-administration, AM251 (4 mg/kg, IP) was injected 30 min before the start of session 21. This dose of AM251 is effective in reducing food intake [8] and increases dopamine signal amplitude in the striatum while reducing the clearance of dopamine in this area [9]. To minimize the potential stress of the injection procedure, a vehicle injection was administered 30 min before the start of sessions 19 and 20. During extinction sessions, animals only received the vehicle alone after each lever press.

2.6. Statistical analysis

Data were analyzed using a mixed ANOVA test with Sessions as the within-subjects factor and Strain as the between-subjects factor. The degrees of freedom were corrected using the Greenhouse-Geisser correction when the assumption of sphericity was not met, and square root transformations were applied in cases where homogeneity of variance was not observed for a given variable. To analyze the Strain $\times$ Session interaction, Bonferroni-corrected pairwise comparisons were performed across sessions. As a measure of effect size, we took the partial η^2 index (% of the variance explained by the significant effect). To analyze the time course of lever pressing during the different phases of the self-administration experiment, we used polynomic contrasts. The effects of AM251 in each strain were further analyzed using the "Difference" contrast (which compares each level of the within-subjects factor with the previous one) in SPSS Statistics software (version 19.0; IBM Corporation, NY, USA). Related-samples t-tests were used to analyze the differences between active and inactive lever presses in each session and for each strain and the r index was used to measure the effect size.

Graphics were prepared with Prism (version 5; GraphPad Software, San Diego, CA, USA). All calculations were performed using the SPSS software and the level of significance was set to $\alpha = 0.05$.

3. Results

3.1. Acquisition

During acquisition, we detected a significant effect of the Sessions factor ($F_{7,217} = 23.499$, $P < .001$) and a significant Strain $\times$ Sessions interaction ($F_{7,217} = 2.631$, $P < .05$). The Sessions factor explained 43.1% of the variance in active

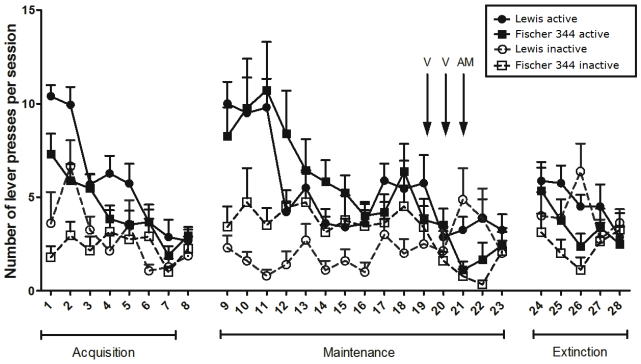

Figure 1: WIN self-administration. The mean number active and inactive lever presses by LEW and F344 rats are shown in each phase (acquisition, maintenance, and extinction). V = vehicle administration. AM = AM251 administration.

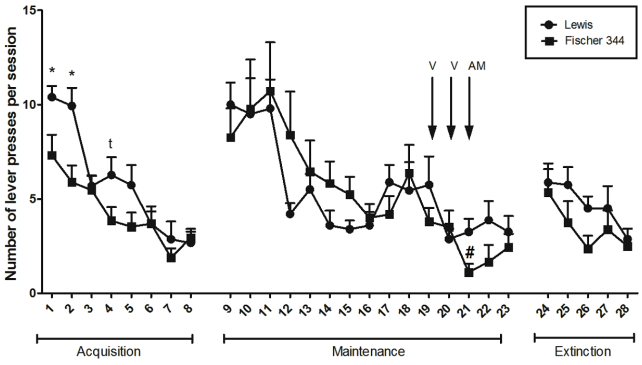

Figure 2: Active lever presses for each phase. *Significant strain difference ($P < .05$). t = trend. #Significant difference versus session 20 ($P < .05$).

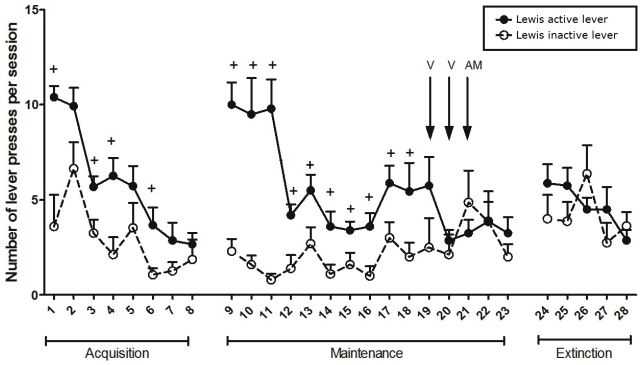

Figure 3: Active and inactive lever presses for each phase by LEW rats. V = vehicle administration. AM = AM251 administration. +Significant difference between active and inactive lever presses ($P < .05$).

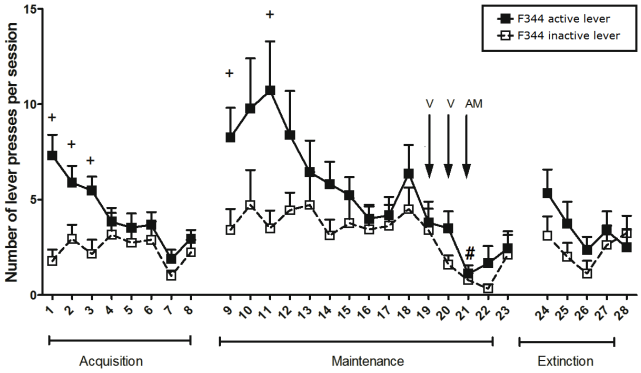

Figure 4: Active and inactive lever presses for each phase by F344 rats. V = vehicle administration. AM = AM251 administration. +Significant difference between active and inactive lever presses ($P < .05$). #Significant difference versus session 20 ($P < .05$).

lever presses, while although significant, the Strain × Sessions interaction only explained 7.3% of the variance. However, the significant between-subjects factor Strain ($F_{1,31} = 183.730$, $P < .05$) explained 12.7% of the variance in active lever presses. Analysis of the Strain × Sessions interaction using a Bonferroni pairwise correction revealed significant strain differences in sessions 1 ($P < .05$) and 2 ($P < .05$), and a strong trend towards significance in session 4 ($P = .052$). In all cases, the number of active lever presses by LEW rats was greater than those performed by F344 rats (see Figures 1 and 2).

During acquisition there was a progressive decay in lever presses in both strains, an effect demonstrated by significant linear and quadratic trends that explained 75.4% and 12.7% of the variance in lever presses across sessions, respectively ($F_{1,31} = 94.913$, $P < .001$ and $F_{1,31} = 4.506$, $P < .05$). Analysis of inactive lever presses revealed a significant Sessions effect ($F_{7,203} = 2.732$, $P < .05$), which explained 8.6% of the variance. A trend analysis demonstrated a significant effect of the linear and fifth-grade components ($F_{1,29} = 5.330$, $P < .05$ and $F_{1,29} = 9.938$, $P < .01$), which explained 15.5% and 25.5% of the variance, respectively. LEW rats significantly discriminated between active and inactive levers in sessions 1, 3, 4, and 6 ($t_{14} = 3.950$, $P < .01$, $r = 0.73$; $t_{15} = 3.084$, $P < .01$, $r = 0.62$; $t_{14} = 3.050$, $P < .01$, $r = 0.63$; $t_{14} = 2.321$, $P < .05$, $r = 0.53$, resp.—see Figure 3). By contrast, F344 rats significantly discriminated between levers in sessions 1, 2, and 3 ($t_{18} = 5.671$, $P < .001$, $r = 0.80$; $t_{18} = 2.722$, $P < .05$, $r = 0.54$; $t_{18} = 3.759$, $P < .05$, $r = 0.66$, resp.—see Figure 4).

3.2. Maintenance

After the first eight days of acquisition, the session duration was increased to two hours. During this phase, a significant Sessions effect was detected for active lever presses ($F_{9,207} = 8.079$, $P < .001$), which explained 26% of the variance in this variable. Analysis of the time course

of active lever presses revealed a progressive decay in this phase (significant linear trend $F_{1,23} = 15.867$, $P < .01$), which explained 40.8% of the variance. Interestingly, a small increase in active lever presses was observed in the final maintenance sessions, an effect that was consistent with the significant quadratic component ($F_{1,23} = 20.561$, $P < .001$) observed for this variable. This latter component explained 47.2% of the variance. The seventh-grade component was also significant ($F_{1,23} = 5.504$, $P < .05$) and explained 19.3% of the variance. No significant effects were detected for inactive lever presses for the within-subjects factor Sessions or the Sessions × Strain interaction. However, a significant effect was detected for the between-subjects factor Strain ($F_{1,23} = 4.551$, $P < .05$), indicating that F344 rats pressed the inactive lever more often than LEW rats during the maintenance phase (mean inactive lever presses $= 1.588 \pm 0.164$ and 1.006 ± 0.219 for F344 and LEW rats, resp.—see Figure 2). However, this effect only explained 16.5% of the variance, suggesting that WIN-reinforced lever pressing is not acquired as readily by F344 rats as by LEW rats. To confirm this finding, we analyzed the differences between active and inactive lever presses per session in both strains. LEW rats pressed the active lever significantly more often than the inactive lever in all sessions of the maintenance phase (session 9: $t_9 = 6.505$, $P < .001$, $r = 0.91$; session 10: $t_9 = 4.001$, $P < .01$, $r = 0.80$; session 11: $t_9 = 5.444$, $P < .001$, $r = 0.85$; session 12: $t_9 = 4.882$, $P < .01$, $r = 0.85$; session 13: $t_9 = 2.838$, $P < .01$, $r = 0.69$; session 14: $t_9 = 3.337$, $P < .01$, $r = 0.74$; session 15: $t_9 = 2.946$, $P < .05$, $r = 0.70$; session 16: $t_9 = 7.005$, $P < .001$, $r = 0.92$; session 17: $t_9 = 5.508$, $P < .05$, $r = 0.88$; session 18: $t_8 = 2.542$, $P < .05$, $r = 0.67$—see Figure 3), while F344 rats only pressed the active lever more often than the inactive lever in sessions 9 ($t_{17} = 2.759$, $P < .05$, $r = 0.56$) and 11 ($t_{17} = 3.098$, $P < .01$, $r = 0.60$—see Figure 4). These data confirm the significant main effect of the between-subjects factor Strain, clearly indicating that F344 rats did not successfully acquire self-administration behavior or they did discriminate well its rewarding effects because they pressed active and inactive levers at a similar rate.

3.3. AM251 challenge

We next investigated whether a challenge with the CB_1 receptor antagonist/inverse agonist AM251 had any effect on WIN-reinforced lever pressing behavior in each strain. ANOVA of active lever presses during sessions 19, 20, and 21 revealed a significant effect of Sessions ($F_{4,60} = 3.367$, $P < .05$) that explained 28% of the variance, and a trend towards significance for the between-subjects factor Strain ($F_{1,15} = 3.458$, $P = .083$) that accounted for 18.7% of the variance—see Figure 1. We then analyzed the time course of lever presses for each strain to look for strain-specific sensitivity to AM251 that may have been masked by the overall variance. The performance of LEW rats was rather stable (no effect of Sessions factor) and when difference contrasts were run, we detected no significant differences for sessions 19, 20 or 21. While the performance of F344 rats was also stable (no significant effects of Sessions factor), the difference contrast revealed a significant difference in the number of lever presses ($F_{1,8} = 15.044$, $P < .01$) in session 21 (when the antagonist was injected) as opposed to session 20 (when vehicle was injected). This effect of the antagonist was long-lasting, as lever press behavior was not recovered in the subsequent test sessions (Figure 2).

No significant effects were observed for inactive lever presses (Figures 1, 3, and 4), although a trend towards significance was detected for the between-subjects factor Strain ($F_{1,15} = 4.096$, $P = .061$; mean inactive lever presses during these sessions $= 3.075 \pm 0.602$ and 1.400 ± 0.568 for LEW and F344, resp.).

3.4. Extinction

After AM251 challenge and two washout sessions (sessions 22 and 23), we studied the extinction of the learned lever-press behavior in both strains by substituting WIN with the vehicle alone. An initial nonsignificant increment in lever presses was observed in both strains as compared with the final test session of the maintenance phase (Figures 1 and 2). During extinction, a significant effect of the Sessions factor was observed ($F_{4.56} = 4.777$, $P < .01$), which explained 25.4% of the variance and confirmed the decay in lever presses across sessions. No other significant effects were observed.

4. Discussion

In light of the previously observed differences in the endocannabinoid system between strains [6,5], we investigated the effects of these differences on cannabinoid self-administration. Neither LEW nor F344 rats acquired a stable WIN self-administration behavior. We observed a significant decay in lever-press behavior throughout the acquisition sessions and when session duration was increased during the maintenance phase, both strains attained higher lever-press rates, although this effect was transient and diminished as the sessions progressed. It is unclear why these two strains failed to stably acquire WIN self-administration. In the present study, we followed a procedure described previously [7], particularly with regards to dose (12.5 μg/kg), food-restriction (throughout the entire experiment), and the reinforcement schedule used (fixed ratio 1). However, certain differences between the protocols used in distinct studies may explain the lack of stable self-administration in our experimental conditions. For example, we used session durations of one hour during

acquisition and two hours during maintenance, distinct from the three-hour sessions used throughout the entire study by Fattore et al. [7]. Other parameters that differed between the two studies were the time-out duration, infusion length, and light cycle, although we previously achieved stable cocaine and morphine self-administration using the same parameters as employed here.

Strain appears to be a crucial factor in explaining the failure of LEW and F344 rats to achieve robust cannabinoid self-administration, as has been reported previously. For example, a recent study found that while Long-Evans and Lister-Hooded rats successfully acquired WIN self-administration, Sprague-Dawley rats failed to reach the acquisition criterion [10]. We found some strain differences in terms of the number of active lever presses at the beginning of the procedure, although this may have been due to the particular training method employed during the first two acquisition sessions (baiting the active lever with a food pellet). It is possible that WIN exposure in LEW rats strengthened food-lever press associations to a greater extent than in F344 rats. Indeed, the cannabinoid system has been shown to participate in the control of food-rewarded operant performance [11,12,13,14], although this effect quickly disappeared in our experimental conditions.

During the maintenance phase, LEW rats displayed better reward-lever discrimination than F344 rats, in part because the number of inactive lever presses was slightly higher in F344 rats. However, this increase in inactive lever presses is unlikely to have resulted from increased locomotor activity, as WIN exerts well-documented hypokinetic effects [15,16]. Administration of the CB_1 antagonist/inverse agonist AM251 significantly decreased active lever presses in F344 but not LEW rats. As such, it could be concluded that WIN reinforced-behavior is only dependent on CB_1 receptors in F344 rats, perhaps due to the decreased expression of these receptors in the PFc of this strain. Indeed, the effects of CB_1 receptor blockade may be enhanced when the number of CB_1 receptors is diminished. Another possible explanation is that AM251 exerts a differential effect on GPR55 receptors. AM251 acts as an agonist at these receptors [17], yet given that the expression of this gene is comparable in the PFc and NAcc of both LEW and F344 rats, this explanation seems unlikely.

When WIN was substituted by the vehicle alone during the extinction phase, we observed a nonsignificant increase in lever-pressing behavior, although no significant strain differences were detected. Interestingly, lever presses decreased during this phase, suggesting that in both strains WIN acts as a reinforcer, at least to some extent.

In summary, although there was not a clear WIN self-administration behavior, LEW rats displayed more active lever presses during acquisition. Interestingly, CB_1 antagonism/inverse agonism appeared to only affect active lever presses in F344 rats, an effect that may be related to the previously reported enhanced NAPE-PLD/FAAH ratio and/or the diminished CB_1 receptor gene transcription observed in this strain. Further studies will be required to compare the actual endocannabinoid content in specific areas of the reward system in both strains to corroborate these findings. Given that LEW and F344 rats are used to model genetic components underlying vulnerability to addiction, our findings suggest that there might be subtle differences in the sensitivity to cannabinoid rewarding effects that might contribute to interindividual differences in cannabinoid use and/or abuse in humans.

Conflict of interest The authors declare that they have no conflict of interest.

References

[1] G. R. Uhl, T. Drgon, C. Johnson, O. O. Fatusin, Q. R. Liu, C. Contoreggi, et al., *"Higher order" addiction molecular genetics: Convergent data from genome-wide association in humans and mice*, Biochem Pharmacol, 75 (2008), 98–111.

[2] C. Cadoni, *Fischer 344 and Lewis rat strains as a model of genetic vulnerability to drug addiction*, Front Neurosci, 10 (2016), 13.

[3] A. Higuera-Matas, G. L. Montoya, S. M. Coria, M. Miguéns, C. García-Lecumberri, and E. Ambrosio, *Differential gene expression in the nucleus accumbens and frontal cortex of Lewis and Fischer 344 rats relevant to drug addiction*, Curr Neuropharmacol, 9 (2011), 143–150.

[4] P. Sánchez-Cardoso, A. Higuera-Matas, S. Martín, N. del Olmo, M. Miguéns, C. García-Lecumberri, et al., *Modulation of the endogenous opioid system after morphine self-administration and during its extinction: A study in Lewis and Fischer 344 rats*, Neuropharmacology, 52 (2007), 931–948.

[5] P. Rivera, M. Miguéns, S. M. Coria, L. Rubio, A. Higuera-Matas, F. J. Bermúdez-Silva, et al., *Cocaine self-administration differentially modulates the expression of endogenous cannabinoid system-related proteins in the hippocampus of Lewis vs. Fischer 344 rats*, Int J Neuropsychopharmacol, 16 (2013), 1277–1293.

[6] S. M. Coria, D. Roura-Martínez, M. Ucha, M. A. Assis, M. Miguéns, C. García-Lecumberri, et al., *Strain differences in the expression of endocannabinoid genes and in cannabinoid receptor binding in the brain of Lewis and Fischer 344 rats*, Prog Neuropsychopharmacol Biol Psychiatry, 53 (2014), 15–22.

[7] L. Fattore, G. Cossu, C. M. Martellotta, and W. Fratta, *Intravenous self-administration of the cannabinoid CB1 receptor agonist WIN 55,212-2 in rats*, Psychopharmacology (Berl), 156 (2001), 410–416.

[8] P. J. McLaughlin, K. M. Winston, C. L. Limebeer, L. A. Parker, A. Makriyannis, and J. D. Salamone, *The cannabinoid CB1 antagonist AM 251 produces food avoidance and behaviors associated with nausea but does not impair feeding efficiency in rats*, Psychopharmacology (Berl), 180 (2005), 286–293.

[9] D. A. Price, W. A. Owens, G. G. Gould, A. Frazer, J. L. Roberts, L. C. Daws, et al., *CB_1-independent inhibition of dopamine transporter activity by cannabinoids in mouse dorsal striatum*, J Neurochem, 101 (2007), 389–396.

[10] S. Deiana, L. Fattore, M. S. Spano, G. Cossu, E. Porcu, P. Fadda, et al., *Strain and schedule-dependent differences in the acquisition, maintenance and extinction of intravenous cannabinoid self-administration in rats*, Neuropharmacology, 52 (2007), 646–654.

[11] M. Arnone, J. Maruani, F. Chaperon, M. H. Thiébot, M. Poncelet, P. Soubrié, et al., *Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors*, Psychopharmacology (Berl), 132 (1997), 104–106.

[12] G. Colombo, R. Agabio, G. Diaz, C. Lobina, R. Reali, and G. L. Gessa, *Appetite suppression and weight loss after the cannabinoid antagonist SR 141716*, Life Sci, 63 (1998), PL113–PL117.

[13] C. S. Freedland, J. S. Poston, and L. J. Porrino, *Effects of SR141716A, a central cannabinoid receptor antagonist, on food-maintained responding*, Pharmacol Biochem Behav, 67 (2000), 265–270.

[14] P. J. McLaughlin, K. Winston, L. Swezey, A. Wisniecki, J. Aberman, D. J. Tardif, et al., *The cannabinoid CB1 antagonists SR 141716A and AM 251 suppress food intake and food-reinforced behavior in a variety of tasks in rats*, Behav Pharmacol, 14 (2003), 583–588.

[15] D. R. Compton, L. H. Gold, S. J. Ward, R. L. Balster, and B. R. Martin, *Aminoalkylindole analogs: cannabimimetic activity of a class of compounds structurally distinct from delta 9-tetrahydrocannabinol*, J Pharmacol Exp Ther, 263 (1992), 1118–1126.

[16] N. A. Darmani, *The cannabinoid CB_1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2*, Eur J Pharmacol, 430 (2001), 49–58.

[17] R. G. Pertwee, *GPR55: a new member of the cannabinoid receptor clan?*, Br J Pharmacol, 152 (2007), 984–986.