doi:10.4149/endo_2015_03_131

Inhibition of fatty-acid amide hydrolyse (FAAH) exerts cognitive improvements in male but not female rats

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Objectives. The endocannabinoid system is implicated in the regulation of various brain functions including cognition, memory, and behavior. It has been shown that inhibition of the endocannabinoid-degrading enzyme fatty acid amid hydrolase (FAAH) enhances the memory and learning in males. Given the fact that sexual dimorphism exists in the different components of the endocannabinoid system, the aim of this study was to test the hypothesis that cognition enhancing effect of the acute inhibition of FAAH by URB597 is gender dependent.

Methods. In the study, 32 adult male and female Sprague-Dawley rats were used. They were treated with a single intraperitoneal injection of FAAH inhibitor URB597 (0.3 mg/kg) or vehicle 40 min before behavioral testing. The novel object recognition test was used as a working memory task to assess cognitive performance.

Results. Neither the treatment nor the gender significantly affected the velocity, the total distance travelled and the time spent exploring the familiar object. The recognition of the object was influenced by both URB597 and gender. Male rats treated with URB597 displayed significantly increased novel object exploration compared to males treated with vehicle as well as to female rats treated with URB597. Single administration of URB597 significantly enhanced the recognition index in male, but not female rats.

Conclusions. The results demonstrate that the positive effects of FAAH inhibition on the cognition are gender dependent. It is likely that male rats are more vulnerable to the modulation of the endocannabinoid system than female rats.

Key words: endocannabinoid system, cognition, gender, URB597

The endocannabinoid system is a neuromodulatory system with an important role in the regulation of various functions, including mood and cognition. The endocannabinoid system is composed of at least two G-protein coupled cannabinoid receptors (CB1 and CB2), their endogenous lipid ligands (endocannabinoids), of which anandamide and 2-arachidonoylglycerol are the best known, and the enzymatic machinery for their biosynthesis and inactivation (De Petrocellis and Di Marzo 2009). Endocannabinoids are not stored but generated "on demand" and degraded by two specific enzymatic systems: the fatty acid amide hydrolase (FAAH) (Cravatt et al. 1996) and monoacylglyceride lipase (Dinh et al. 2002).

Endocannabinoid signaling can be enhanced by administering an enzyme inhibitor that prevents the breakdown of endocannabinoids released (Zanettini et al. 2011). FAAH is the primary catabolic enzyme of the

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main endocannabinoid anandamide. Various classes of FAAH inhibitors have been developed so far. A highly potent and selective inhibitor of FAAH, the compound named URB597, rapidly increases the brain anandamide levels and has no affinity for cannabinoid CB1 receptors (Piomelli et al. 2006). URB597 does not evoke psychotropic and other classical cannabinoid-like effects (e.g. catalepsy, hypothermia, hyperphagia), but does exert analgesic (Jhaveri et al. 2006), anxiolytic-like (Moreira et al. 2008; Scherma et al. 2008), and antidepressant effects (Bortolato et al. 2007; Adamczyk et al. 2008).

There is a general agreement that activation of the endocannabinoid system by cannabis or endocannabinoid anandamide induces cognitive deficits in humans and laboratory animals (Riedel and Davies 2005; Ranganathan and D´Souza 2006; Morena and Campolongo 2014). It has been shown that anandamide-induced memory disruption is mediated by CB1 receptors (Mallet and Beninger 1998). On the other hand, there are contradictory findings showing that increasing endogenous levels of anandamide and facilitating endocannabinoid signaling by FAAH inhibition can enhance the learning and memory in various cognitive tasks (Varvel et al. 2007; Zanettini et al. 2011; Hasanein and Teimuri Far 2015).

The novel object recognition test is a working memory task which utilizes the natural tendency of rodents to explore novel items more than the familiar ones (Ennaceur and Delacour 1988). The recognition of novelty requires enhanced cognitive skills from the subject. The novel object recognition test represents sensitive procedure for measuring cognitive performance, identification of the cognitive deficits as well as testing the efficacy of novel therapeutic agents (Grayson et al. 2015). Generally, cognition and memory enhancing drugs increase the time of novel object exploration.

The gender impact on the novel object recognition test performance is not fully clarified. One evolutionary scenario is suggesting a female foraging hypothesis, according to which the females should, in the remembering the identity of objects, be better than males, which is particularly relevant to the novel object recognition paradigm (Sutcliffe et al. 2007; Saucier et al. 2008). This suggestion is supported by findings on positive influence of ovarian steroids in enhancing object recognition in rats (Walf et al. 2006; Vedder et al. 2013).

It has been shown that a sexual dimorphism exists in different components of the endocannabinoid system (Rubino and Parolaro 2011). Since, there is no study available, evaluating the possible gender differences in response to FAAH inhibition in relation to cognition, the aim of this study was to verify the hypothesis that cognition enhancing effect of the acute inhibition of the endocannabinoid-degrading enzyme FAAH by URB597 is gender dependent.

Material and Methods

Animals. Adult male (n=16) and female (n=16) Sprague-Dawley rats (AnLab s.r.o., Prague, Czech Republic) aged 10 weeks (200-225 g) were used in this study. They were housed two per cage in standard polycarbonate cages with sawdust bedding and free access to food and water. They were kept in a temperature (22±2°C) and humidity controlled room. Lights were maintained on a reverse 12:12 h light/dark cycle (lights on at 19:00 h), with all behavioral procedures occurring during the dark period of the light/dark cycle. Rats were acclimated to the housing conditions for 2 week before experiments and were handled daily by an experimenter. All experimental procedures were approved by the Animal Health and Animal Welfare Division of the State Veterinary and Food Administration of the Slovak Republic and conformed to the NIH Guidelines for Care and Use of Laboratory Animals.

Drugs. URB597 (Sigma-Aldrich, Slovakia) or vehicle was administered by a single intraperitoneal (i.p.) injection. The dose of URB597 (0.3 mg/kg body weight) was chosen on the basis of previous studies (Bortolato et al. 2007; Hill et al. 2007). URB597 was dissolved in dimethyl sulfoxide (DMSO), Tween 80 and saline (1:1:8, respectively) and injected in a volume of 1 ml/kg. Control rats were injected with vehicle only (1:1:8 DMSO, Tween80, saline).

Novel object recognition test. The novel object recognition test was performed as described by Ennaceur and Delacour (1988) with some modifications according to Jensen et al. (2014). The apparatus was a squared arena (49 x 49 x 37 cm) made from black polyvinyl chloride. The novel object recognition test lasted 2 days and consisted of 3 phases: 1) *Habituation* session comprised placing the rat into the centre of an empty testing arena allowing it to freely explore for 5 minutes, 2) *Training session* was conducted 24 h after habituation. Each rat was rehabituated to the arena for 1 min. Thereafter, two identical objects were presented to the animal. The rat was allowed to freely explore the objects for 15 min. Upon completion, the rat was returned to its home cage. 3) *Test session* occurred 45 min after finishing the training session. One of the familiar objects was replaced by a novel one with distinctive material,

shape, and color. The rat was returned to the arena and allowed to explore for 3 min. In all sessions, objects were placed in back corner of the arena at a distance of 5 cm from the wall. The objects to be discriminated were made of biologically inert substance (glass, metal and plastic). For each subject, the character and position of the objects was counterbalanced and randomly changed to reduce effects of object and place preference. The arena and objects were cleaned and dried after each trial. The movement of the rat was continuously tracked and recorded using a video camera attached to a computer running Noldus Ethovision XT program. Exploration was defined as the rat directing its nose toward an object within a distance of 1 cm and/or touching the object. Climbing or sitting on the object was not considered as exploration. The time spent in the exploration of the novel object (N), familiar object (F), and both objects (i.e. the total object exploration time) were calculated. A recognition index was calculated for each animal as a percentage of time spent exploring novel object relative to the total time exploring both objects during the test session [N/(N + F) x 100].

Experimental design. On the day 1, animals were given a habituation session of the novel object recognition test. On the day 2, rats from both genders were randomly assigned into two treatment groups (n=8 rats/group) and received a single i.p. injection of URB597 or vehicle. Forty min following the injection of their respective treatment, animals were subjected to the training session followed by the test session of the novel object recognition test. One hour prior behavioral testing, the animals were transported to the experimental room for acclimation. All testing occurred between 08:30 and 11:30 h, during the dark/active phase of the light/dark cycle.

Statistical analysis. Data were checked for normality of distribution by the Shapiro-Wilk test. For statistical analysis, two-way ANOVA with factors treatment and gender was used. Whenever interaction reached significance, the Tukey *post hoc* test was performed. Results are expressed as mean ± SEM values. Overall level of significance was defined as $p<0.05$.

Results

Statistical analysis by two-way ANOVA did not show any effect of treatment or gender on the velocity and the total distance travelled during the test session. No significant main effect of gender on the time spent in exploring the familiar object was observed. There was a tendency to spent more time exploring the familiar object in animals treated with vehicle compared to those treated with URB597, however, the difference did not reach statistical significance ($F_{(1, 26)}=3.90$, $p=0.058$) (Fig. 1).

Two-way ANOVA revealed a significant main effect of treatment ($F_{(1, 26)}=7.53$, $p=0.011$) and gender ($F_{(1, 26)}=4.24$, $p=0.049$) on the novel object exploration (Fig. 2). Both the male gender and the administration of URB597 increased exploration time of the novel object. There was also significant interaction between treatment and gender ($F_{(1, 26)}=5.10$, $p=0.033$). Tukey *post-hoc* comparisons revealed significantly increased novel object exploration in male rats treated with URB597 in comparison with male rats treated with vehicle ($p=0.006$), as well as female rats treated with URB597 ($p=0.032$).

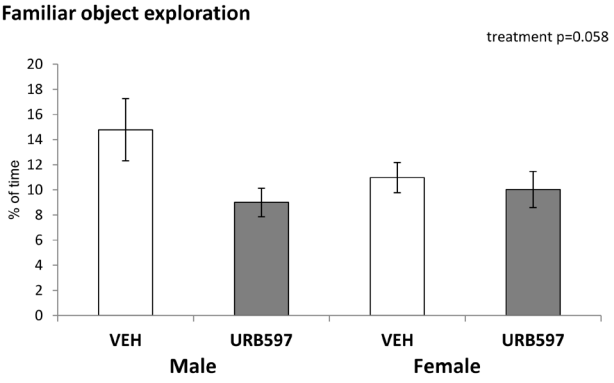

Fig. 1. The effects of gender and URB597 on the time spent in exploring the familiar object. Data are expressed as means ± SEM (n=8/group). Statistical significance as revealed by two-way ANOVA.

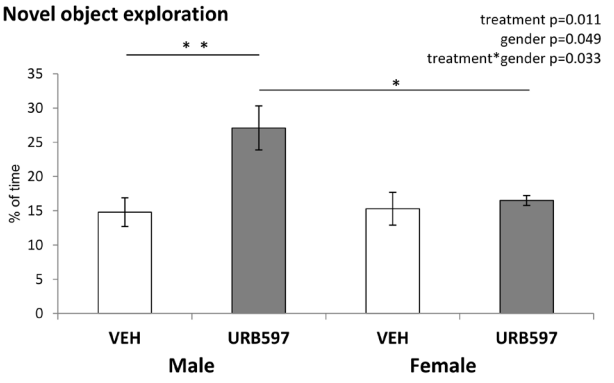

Fig. 2. The effects of the gender and URB597 on the time spent in exploring the novel object. Data are expressed as means ± SEM (n=8/group). Statistical significance as revealed by two-way ANOVA followed by Tukey-*post hoc* as appropriate.

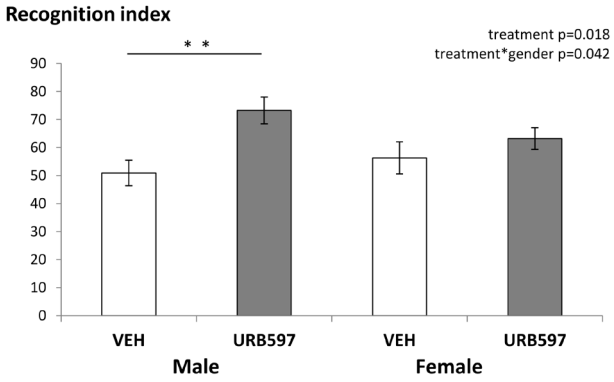

Fig. 3. The effects of the gender and URB597 on the recognition index. Data are expressed as means ± SEM (n=8/group). Statistical significance as revealed by two-way ANOVA followed by Tukey-*post hoc* as appropriate.

Statistical analysis showed a significant main effect of treatment ($F_{(1, 26)}$=6.37; p=0.018) on the recognition index (Fig. 3). This memory index was not influenced by gender. Two-way ANOVA revealed significant treatment x gender interaction ($F_{(1, 26)}$=4.55, p=0.042). Further analysis demonstrated that single administration of URB597 significantly enhanced the recognition index in male (p=0.013), but not in female rats.

Discussion

The present findings provide the first evidence on a gender dependent effect of FAAH inhibition on the cognitive functions. Our results showed that the enhancement of the endocannabinoid signaling induced by a single administration of FAAH inhibitor URB597 may elicit cognitive improvements in male gender only.

Males and females treated with vehicle exhibited a similar preference for the novel object during the test session. These results failed to confirm previous findings by Sutcliffe et al. (2007) and Saucier et al. (2008) that female rats show improved object recognition memory compared to males. This discrepancy may be due to a different test protocol of the test employed, particularly regarding the number of training sessions, as well as the retention interval between the training and test session. Another possibility is the influence of strain differences. It is well known that different strains of rats and mice may have diverse behavioral outcomes, which are thought to be due to their underlying genetic background (Hlavacova et al. 2006; Yilmazer-Hanke 2008; van Goethem et al. 2012). Sutcliffe et al. (2007) and Saucier et al. (2008) have used Lister and Long-Evans rats, while we have investigated rats of Sprague-Dawley strain. The present data do not support the female foraging hypothesis.

In male animals, we have observed that inhibition of FAAH results in the improvements of cognitive function, which is in accordance with the previous findings in male rats or mice. It has been demonstrated that elevating brain concentrations of FAAH, via either genetic deletion or pharmacological blockade of FAAH, facilitated the extinction of spatial memory task (Varvel et al. 2007) and enhanced the memory acquisition in passive-avoidance task (Varvel et al. 2007; Mazzola et al. 2009). Recently, Hasanein and Far (2015) have reported dose dependent enhancing effects of URB597 on recognition memory in the novel object recognition test and on acquisition in passive avoidance learning test in male Wistar rats. They argued that the positive effect of URB597 might be dependent on CB1 receptors. Mazzola et al. (2009) have suggested that improvement in learning and memory, induced by FAAH inhibition, might be mediated via interaction between the endocannabinoid system and peroxisome proliferator-activated receptor-α (PPAR-α). Endocannabinoids, including anandamide, act as endogenous ligands of PPAR-α (Mackie and Stella 2006; O´Sullivan et al. 2007; Sun et al. 2007) and PPAR-α has been shown to play an important role in the learning and memory processes (Mazzola et al. 2009).

The memory enhancing effects of URB597 are not likely to be attributed to potential effects on general locomotion, as the treatment with URB597 failed to modify the velocity and the total distance travelled. This was observed in the present study as well as studies reported by others (Scherma et al. 2008; Mazzola et al. 2009; Hanasein and Teimuri Far 2015).

The main finding of the present study is that the acute administration of FAAH inhibitor URB597 increased the exploration of the novel object and enhanced the recognition index in male but not female rats. The mechanisms by which URB597 induced gender dimorphic effects in cognitive performance in the present experiments are unknown, but there are several factors which might contribute to this phenomenon. Sexual dimorphism exists in almost all components of the endocannabinoid system (Rubino and Parolaro 2011). Density of CB1 receptors has been found to be higher in adult males compared to females in several brain regions (Rubino et al. 2008; Burston et al. 2010; Riebe et al. 2010). As the effects of URB597 on cognition improvement were suggested to be mediated

via CB1 receptors (Hasanein and Teimuri Far 2015). The presence of higher density of brain CB1 receptors in males could be one of the possible mechanisms. Another explanation could arise from the observation that female rats exhibited higher gene expression of FAAH in the frontal cortex than males (Marco et al. 2014). We can hypothesize that the dose of URB597 used in the present experiments was not sufficient to inhibit FAAH in females, while it was effective in males. Further studies are needed to evaluate the dose-response relationships.

In conclusion, the present results demonstrate that the improvement in cognitive function induced by FAAH inhibition is gender dependent. It is likely that males are more vulnerable to the modulation of the endocannabinoid system which affects cognitive performance. Additional information on the mechanisms responsible for gender dimorphism in endocannabinoid signaling is needed before the pharmacological blockade of the endocannabinoid-degrading enzyme could be considered as a target for the future development of cognition enhancing drugs.

Acknowledgements

This study was supported by the grant scheme Establishment of Academic Science Park for Biomedicine Bratislava, code ITMS 26240220087.

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