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Research article

The impact of sleep deprivation on sexual behaviors and FAAH expression in the prefrontal cortex of male rats

Mohammad Amini^a, Ehsan Saboory^{b,*}, Leila Derafshpour^a, Ali Fakhari^c, Joseph C. Wu^d, Richard Bruggeman^e, Fatemeh Asgharzadeh^a, Ali Ahmadalipour^{c,**}

^a Neurophysiology Research Center, Urmia University of Medical Sciences, Urmia, Iran

^b Zanzan Metabolic Diseases Research Center, Zanzan University of Medical Sciences, Zanzan, Iran

^c Research Center of Psychiatry and Behavioral Sciences, Aging Research Institute, Tabriz University of Medical Sciences, Tabriz, Iran

^d UC Irvine Department of Psychiatry and Human Behavior, Irvine, CA 92697, United States

^e University of Groningen, University Medical Center Groningen, Department of Psychiatry, Rob Giel Research Center, the Netherlands

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ABSTRACT

Sleep deprivation (SD) causes alterations in the function of the endocannabinoid (EC) system and also results in alteration in many behaviors such as increased anxiety, deteriorated alertness, memory deficits, as well as sexual behaviors. Controversial data about the effects of SD on sexual response are provided. Fatty acid amide hydrolase (FAAH), the enzymes involved in the degradation of the EC system play an important role in the function of the EC system. This study aimed to investigate the effect of REM SD (RSD) and total SD (TSD) on the sexual behaviors and FAAH expression in the prefrontal cortex (PFC) of male rats. RSD was carried out through the flower pot technique for 24 h and 48 h, and TSD also was induced by keeping awake the rats by gentle handling for 6 h. Immediately after RSD and TSD, sexual behaviors were recorded for 45 min. Sexual behaviors were reduced by both types of RSD and TSD. The deleterious effects of 24 h RSD were more severe compared with 6 h of TSD. Serum testosterone concentration was significantly higher after TSD but not RSD compared to the normal sleep (NS) group. FAAH expression in the PFC was significantly reduced after both RSD and TSD compared to the NS group. Given that the function of the EC system has been previously shown to change different behaviors such as sexual activity, our results could suggest that behavioral effects of both types of SD on sexual behavior may partially result from activation of this signaling pathway by the reduction of FAAH in the PFC.

1. Introduction

Although sleep is an evolutionarily conserved behavior, its functions and mechanisms are still argued. Many aspects of modern life such as electric lights, television and computer screens, longer commutes, the blurring of the line between work and personal time, using cell phones to scroll through social media and so on, have contributed to sleep deprivation (SD), which has been shown to be linked to many health problems. It is shown that SD is associated with sexual problems such as erectile dysfunction [1] and sexual motivation [2], although the reports about the effects of SD on sexual response in animal models are controversial [3] and little is known about the exact mechanisms of altered sexual behavior after SD.

Sexual activity is a natural rewarding behavior [4] and it is shown that SD is associated with activation of the endocannabinoid (EC) system which plays important role in the regulation of rewarding behaviors [5]. In addition, it is shown that the activated EC system is associated with some of the effects of SD, such as excessive food intake and increased risk of obesity [6,7]. This system mediates the effects of cannabis and its derivatives such as marijuana and hashish which is also shown to affect sexual behavior. The EC system is involved in several physiological functions, not only in the central nervous system but also in the autonomic nervous system, the immune system, the endocrine network, the reproductive system, and the gastrointestinal tract. EC system acts through CB1 and CB2 receptors and synaptic levels of the ECs are in part controlled by FAAH, which terminates the activity of

Abbreviations: SD, sleep deprivation; ECs, endocannabinoid system; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; FAAH, fatty acid amide hydrolase; 2-AG, 2-arachidonoylglycerol; AEA, N-arachidonylethanolamide; MAGL, monoacylglycerol lipase; PFC, prefrontal cortex; RSD, REM sleep deprivation; TSD, total sleep deprivation; NS, normal sleep

* Corresponding author at: Zanzan Metabolic Diseases Research Center, Zanzan University of Medical Sciences, Zanzan, zip code: 45157-77978, Iran.

** Corresponding author at: Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran.

E-mail addresses: saboory@zums.ac.ir (E. Saboory), alipoura@tbzmed.ac.ir (A. Ahmadalipour).

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anandamide and can also hydrolyze other endocannabinoids including 2-AG and the sleep-inducing substance, oleamide [8]. Nevertheless, FAAH is necessary for regulating of AEA and other fatty acid amide signaling [9]. Anandamide and oleamide are fatty acid amides involved in the regulatory mechanisms of sleep processes [10], anandamide affects sexual and reproductive activities [11], and FAAH inhibitors exert wake-modulating effects such as arousal and alertness [12]. Recently, many pieces of evidence indicate the existence of an interplay between the EC system and sex hormones. EC system exerts biphasic effects on several behaviors; some findings suggest they inhibit male sexual behavior, and some studies show they can facilitate male rat sexual behavior [4].

Several brain regions are implicated in sexual behavior processing. Prefrontal cortex serves in an executive capacity to regulate sexual behavior consistent with its role in other forms of cognition, emotion, and behavior [13]. This part of brain is an important area for synthesizing information about sensory input, reward availability and valence, and translating those data into behavioral action. Human studies have shown that the PFC might process sensory and visual information about a potential sexual opportunity [14]. It is shown that SD alters synaptic and intrinsic neuronal properties in mouse PFC [15] however, less is known about the EC system activity in the PFC and its relationship with alteration of sexual behavior after different kinds of SD. It can be hypothesized that as a consequence of SD, the activity of EC system can be increased partly by reduction of FAAH expression and could mediate the broad effects of SD including altered sexual behavior. Therefore, in the current study, we examined the effects of RSD and TSD on sexual behavior and the expression of FAAH in the PFC in male rats.

2. Materials and methods

2.1. Animals

In this experimental study, 48 adult male Wistar rats (250 ± 50 g; 21 ± 2 °C; the animal facility at Urmia University of Medical Sciences, Urmia, Iran) were housed (light on at 07:00 A.M.). Rats were divided into two groups of behavioral and molecular experiments and each group into three sub-groups of control, TSD and RSD ($n = 8$) with free access to food and water during the experiment. All animals were given five mating trials in the light phase by the polygamous model (a male rat was caged with 2 females, simultaneously (to get sexual experience. Then, they were placed in individual condition for a week. The Regional Medical Ethics Committee in West Azerbaijan province, Iran, approved this study. All the experimental protocols and procedures complied with the guidelines of the Declaration of Helsinki (2008) as reflected in the guidelines of the Medical Ethics Committee, Ministry of Health, Iran.

2.2. Sleep deprivation

The flowerpot technique, despite a few known disadvantages and challenges, including loss of non REM sleep and not complete (100 %) loss of REM sleep, is considered best practice for REM sleep deprivation studies [16]. Thus, the rats were deprived of sleep through the flower pot technique [17]. A single platform was provided in the center of a cage (tank) that is surrounded by water to about one cm below the platform surface. As it is known that the flower pot technique provokes higher levels of stress compared to other procedures for SD, this technique was used for all groups to align conditions. In this regard, the platform size was chosen based on the group. The diameter of platform was 12 cm for control and TSD, 6 cm for RSD. Therefore, TSD was performed in the water-filled cage and the animal was kept awake on the larger platform by gentle handling via soft brush as soon as a tendency to sleep was observed for 6 h (7:00-13:00). RSD was carried out during 24 and 48 h; because of atonia in muscles, the rat's muzzle

dropped into the water (due to small size of platform) and awakened it. Finally, control groups were placed on the larger platform where rats could sleep quietly. Sleep experiments were planned to end up in all groups at 13 o'clock, then the rats were subjected to the next experiment immediately. We subjected four rats to experiments each day.

2.3. Sexual behavior

Sexually experienced rats were used in this study. Female rats were housed in the standard condition, four per cage for a week to align the estrus cycle. Each rat was used once a time. After sexual behavior evaluation, female rats were excluded from the experiment. Male rats were placed in the cage five minutes before presenting females. The parameters [18] recorded during sexual behavior for 45 min included: 1. Mount Latency (ML): time from the onset of the test to the first mount with or without penile insertion. 2. Intromission Latency (IL): the time from the introduction of the female to the first intromission. 3. Ejaculation Latency (EL): time from the first intromission to ejaculation. 4. Number of Mount (NM): (mounts with pelvic thrusting). 5. Number of Intromission (NI): (mounts with pelvic thrusting and penile insertion). 6. Number of Ejaculation (NE) 7. Post-Ejaculatory Interval (PEI): time from ejaculation to the first intromission of the second copulatory series. 8. Intromission Ratio (IR): This is a derived parameter obtained by dividing the number of intromissions by the number of mounts plus the number of intromissions. 9. Inter-Intromission Interval: The ejaculation latency divided by the number of intromissions. 10. Copulatory Rate (CR): The number of mounts plus the number of intromissions divided by the time from the first mount until ejaculation, not the ejaculation latency. 11. Mount Frequency (MF): the number of mounts without intromission prior to ejaculation. 12. Intromission Frequency (IF): the number of mounts with intromission before ejaculation. 13. Copulatory Efficiency (CE): a measure of intromission success (calculated as a percentage of mounts in which the male gained vaginal insertion) 14. The sex activity index = $NI + NE / NM + NI + NE$

Notice: we examined Anovaginal latency (latency to first behavior included male's anovaginal smelling and female's reaction) for the diagnosis of estrus cycle in female rats; when a female has a sexual reception, the parameters were measured.

2.4. Elisa (testosterone concentration)

To determine the relationship between sexual behavior and testosterone concentration after dissection, serum obtained following blood centrifugation (1000g, for 10 min, at 4 °C), then stored at -80 °C as far as the analysis. Testosterone level measured via related kit and based on the kit instructions (DiaSorin, Italy).

2.5. Western blot (FAAH in PFC)

To evaluate the level of the FAAH protein assay in the PFC tissues, the PFC was dissected, homogenized and sonicated in buffer consist of (Tris-HCL 500 μ L, PH = 8, EDTA 0.003 g, NaCl 0.08 g, Sodium Deoxycholate 0.025 g, SDS 0.01 g, Protease inhibitor cocktail 1tablet, NP40 (1%) Triton 10 μ L, then centrifuged (1000g, for 10 min, at 4 °C). Proteins were isolated through SDS-PAGE and electrotransferred to nitrocellulose membrane. After blocking, the anti-FAAH antibody was applied. The concentration of the protein was measured. The reaction between the antigen and the antibody density was assessed via alpha view software for fluorchem systems (Santa Cruz Biotechnology, USA).

2.6. Statistical analysis

Data processing was carried out by Microsoft Excel 2016 and IBM SPSS 16. Data are presented as means $\pm$ SE. Because of the absence of normality distribution on sexual behavior parameters, the nonparametric Kruskal Wallis test was used to analyze the data. Dunn's post hoc

Fig. 1. Schematic diagram of the experimental study design.

with Bonferroni adjustment tests were carried out on each pair of groups. One-way ANOVA and post-hoc Tukey test was used to determine the source of detected significant differences in the alterations of testosterone, and FAAH expression in the PFC between groups. The effect size was calculated for significant results in ANOVAs using online test (<https://webpower.psychstat.org/models/means03/sizeeffectsize.php>). Differences with $p < 0.05$ were considered statistically significant (Fig. 1).

3. Results

3.1. SD reduced sexual behavior parameters

There was no sexual behavior among rats of the 48 h RSD group (data are not shown here). Therefore, 48 h RSD was not considered for further experiments. Kruskal-Wallis test provided evidence of a difference ($p < 0.05$) between the values of IL, EL, NI, NE, PEI, IR, CR of studied groups. Dunn's pairwise tests were carried out for the three pairs of groups. There was evidence ($p < 0.05$, adjusted using the Bonferroni correction) of a difference between the RSD and TSD groups versus the NS group. The mean rank different parameters of the sexual activity of groups are shown in Table 1.

3.2. SD reduced sex activity index

In addition, sex activity index of RSD and TSD groups was 0 and 0.12 compared to 0.31 in the control NS group. Kruskal-Wallis test provided evidence of a significant difference ($p = 0.043$) between the groups. Dunn's pairwise tests were carried out for the three pairs of groups. There was evidence ($p = 0.042$, adjusted using the Bonferroni correction) of a difference between the groups of RSD and control NS

Fig. 2. Sexual activity index: * $P < 0.05$, for the groups connected by a straight line using one-way Kruskal-Wallis test with Dunn's post-hoc test.

group. There was no significant difference between the other pairs. The mean different parameters of the sexual activity of groups are shown in Fig. 2.

3.3. SD reduced FAAH expression in the PFC

One-way ANOVA provided very strong evidence of a difference ($F(2,15) = 21.43$, $p = 0.0005$, effect size = 0.48) between groups. A Tukey post hoc test revealed that FAAH expression in the PFC significantly decreased after RSD and TSD compared to the control NS group ($p = 0.0005$ and $p = 0.004$, respectively). There was also a significant difference ($p = 0.046$) between the TSD and RSD groups (Fig. 3A).

Table 1

Effect of sleep deprivation on parameters of sexual activity in rats.

	Variations	Control (NS) Mean Rank	RSD Mean Rank	TSD Mean Rank	P-value (Kruskal-Wallis)	Adj. Sig (p value) Pairwise comparison; Compared with control
1	ML	7.3	14.4	11.14	0.168	–
2	IL	5.4	15 *	11.73	0.016	* RSD (0.015)
3	L.F.Behav	6.4	14.4	11.55	0.095	–
4	EL	4.6	13 *	13 #	0.001 \$	* RSD (0.005); #TSD (0.001)
5	NM	16.2	8.4	9.82	0.074	–
6	NI	16.9	7.5 *	9.91 #	0.01 \$	* RSD (0.01); # TSD (0.03)
7	NE	17.4	9 *	9 #	0.001 \$	* RSD (0.005); # TSD (0.001)
8	PEI	17.4	9 *	9 #	0.001 \$	*RSD (0.005); #TSD (0.001)
9	IR	15.5	7.5 *	10.55	0.048 \$	*RSD (0.04)
10	I-I.I	14.9	7.5	10.82	0.079	–
11	CR	17.4	9 *	9 #	0.001 \$	* RSD (0.005); # TSD (0.001)
12	MF	17.4	9 *	9 #	0.001 \$	*RSD (0.005); # TSD (0.001)
13	IF	17.4	9 *	9 #	0.001 \$	* RSD (0.005); # TSD (0.001)
14	CE	15.1	7.5	10.73	0.067	–

\$ indicates significant difference between the groups by Kruskal-Wallis test; * indicates significant difference between the RSD and control groups; # shows significant difference between the TSD and control groups. Mount Latency (ML); Intromission Latency (IL); Ejaculation Latency (EL); Number of Mount (NM); Number of Intromission (NI); Number of Ejaculation (NE); Post-Ejaculatory Interval (PEI); Intromission Ratio (IR); Inter-Intromission Interval (III); Copulatory Rate (CR); Mount Frequency (MF); Intromission Frequency (IF); Copulatory Efficiency (CE).

Fig. 3. Effect of SD on protein expression of FAAH in the PFC (A) and testosterone concentration (ng/dl) in blood (B); A: * $P < 0.05$, ** $P < 0.005$ for the groups connected by a straight line (one-way ANOVA and Tukey); B: TSD group compared with control (** $P < 0.005$) and RSD (## $P < 0.005$) by one-way ANOVA and Tukey post-hoc test.

3.4. SD altered testosterone concentration (ng/dl) in blood

One-way ANOVA provided very strong evidence of a difference ($F(2,14) = 41.48$, $p = 0.0005$, effect size = 2.27) between groups. A Tukey post hoc test revealed that the mean of serum testosterone concentration was significantly higher after TSD but not RSD compared to the control NS group. There was also a significant difference ($p = 0.001$) between the TSD and RSD groups (Fig. 3.B).

4. Discussion

Although previous studies have established a connection between SD and sexual behaviors, to our best knowledge, this is the first study to analyze the relationship between SD (RSD and TSD), FAAH expression in the PFC, and sexual behaviors in adult male rats. The results demonstrated that both types of SD models of our study reduced sexual behavior and FAAH expression in the PFC. TSD but not RSD increased testosterone level in serum of rats. A previous study reported that the RSD facilitates the sexual response [19], which is in contrast with our findings. Although lack of direct association between testosterone level and sexual behaviors found in earlier works [20] was confirmed inconsistencies with the current results may be explained in part by the different length and protocol of two studies. Here, we applied RSD for 24 h and immediately tested sexual behaviors, however, in the mentioned study, rats were submitted to 6 copulatory tests, each with an interval of 4 days; before the 5th test, the sexually vigorous males were selected to be sleep deprived (RSD) for 96 h before the sexual behavior test [19].

The underlying mechanisms of the SD effects on sexual behaviors remain to be determined. Several regions of the brain that are affected by SD are shown to be involved in sexual activities. PFC serves in an executive capacity to regulate sexual behavior [21] and it is shown that lesions of the medial PFC in male rats (involving anterior cingulate and adjacent areas) reduce mounting, intromission, and ejaculation [22,23]. SD impairs many tasks such as flexible thinking and working memory [24,25], that are considered to be mediated by the PFC [26] and one of the possible mechanisms of these impairments might be the activation of the EC system. Similarly, a study has reported that the inhibition of FAAH is associated with an increase in the anandamide [5]. Our results showed that FAAH expression was significantly reduced after 24 h RSD and 6 h TSD in the PFC. Although some recent findings revealed that anandamide was not altered by sleep loss in human serum [27], decreased FAAH expression may induce sleep as it terminates not only anandamide activity but also some of other long fatty acids of the

EC system such as 2-AG and oleamide [28]. Therefore, reduced sexual activity following RSD and TSD could be associated with reduced FAAH expression in the PFC and reduction of FAAH expression might be responsible for some of the neurobehavioral consequences of SD.

The current results showed that 24 h period of RSD had stronger effects on FAAH expression and sexual activity compared to 6 h of the TSD. However, serum level of testosterone in TSD group was increased very significantly compared to RSD and NS groups and these different effects of TSD and RSD might be explained by biphasic relationship between the FAAH expression and testosterone levels such as those relationships seen between the anandamide and male rat sexual behavior [4,29]. It has been shown that anandamide exerts dose-dependent biphasic effects on the copulatory behavior of sexually experienced male rats and facilitates sexual behavior expression of sexually satiated animals at low doses. On the contrary, after the highest anandamide dose, the anandamide inhibitory effects became evident [11]. As anandamide is degraded by the FAAH and here we studied the expression of FAAH, similar to anandamide biphasic effects, the relationship between FAAH and testosterone can be bidirectional and, in this sense, a moderate decrease in FAAH due to TSD may increase testosterone, but an intense decrease in FAAH due to RSD may reduce testosterone. In addition, a long period of RSD, may induces more stress than TSD and studies suggest that there may be a negative relationship between stress or stress hormones and testosterone levels in body fluids [30,31].

Interestingly, SD is the most widely documented rapid-onset antidepressant therapy [32]. In our study, the antidepressant effect of SD was not studied; however, the result showed an effect of SD similar to that of antidepressant drugs. Decreased sexual behavior after SD (a well-known antidepressant as mentioned above) is consistent with sexual dysfunction after the administration of all antidepressants with serotonergic activity [33]. The facilitation of the EC system is sufficient to produce all of the behavioral and biochemical effects of conventional antidepressant treatments [5]. FAAH can be considered as an important player in this effect, as genetic or pharmacological inactivation of FAAH produces an antidepressant effect [34], a phenotype that is the same as the effects of antidepressants. In this sense, the reduction of FAAH expression (facilitation of the EC system) can result in sexual dysfunction similar to antidepressant drugs. Due to insufficient facilities, this study was limited by the absence of an evaluation of ECs profiles and this would be a fruitful area for further work. We suggest the investigation of the expression of monoacylglycerol lipase (MAGL), the enzyme responsible for the degradation of 2-AG, FAAH activity (we measured the expression level of FAAH) and the PFC levels of anandamide, as well as the impact of SD on 2-AG and its enzyme as well for future studies.

5. Conclusion

Our results suggest that sexual behaviors and the sex activity index are reduced by both RSD and TSD, and sexual behavior dysfunctions after SD appears to be mediated partly by the activation of the EC signaling pathway. Future studies should attempt to replicate the finding that altered sexual behavior as a result of SD may result from alterations in FAAH expression.

Author contributions statement

Mohammad Amini, Ehsan Saboory, and Ali Ahmadelipour had a contribution on design of the work, data acquisition, data analysis, and interpretation, drafting and revising the manuscript; Leila Derafshpour, Ali Fakhari, Joseph C. Wu, Richard Bruggeman, Fatemeh Asgharzadeh had a contribution on design of the work, drafting and revising the manuscript.

Statement of ethics

All procedures performed in studies involving animal subjects were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neulet.2020.135254>.

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