Social Neuroscience

ISSN: 1747-0919 (Print) 1747-0927 (Online) Journal homepage: http://www.tandfonline.com/loi/psns20

Relationship between orexin A and childhood maltreatment in female patients with depression and anxiety

Saliha Ozsoy, Ozlem Olguner Eker, Ummuhan Abdulrezzak & Ertugrul Esel

To cite this article: Saliha Ozsoy, Ozlem Olguner Eker, Ummuhan Abdulrezzak & Ertugrul Esel (2017) Relationship between orexin A and childhood maltreatment in female patients with depression and anxiety, Social Neuroscience, 12:3, 330-336, DOI: 10.1080/17470919.2016.1169216

To link to this article: http://dx.doi.org/10.1080/17470919.2016.1169216

Published online: 04 Apr 2016.

Submit your article to this journal

Article views: 47

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
http://www.tandfonline.com/action/journalInformation?journalCode=psns20

Download by: [Erciyes University] **Date:** 04 April 2017, At: 03:12

SOCIAL NEUROSCIENCE, 2017
VOL. 12, NO. 3, 330–336
http://dx.doi.org/10.1080/17470919.2016.1169216

Routledge
Taylor & Francis Group

Check for updates

Relationship between orexin A and childhood maltreatment in female patients with depression and anxiety

Saliha Ozsoy[a], Ozlem Olguner Eker[b], Ummuhan Abdulrezzak[c] and Ertugrul Esel[a]

[a]Department of Psychiatry, Erciyes University School of Medicine, Kayseri, Turkey; [b]Department of Psychiatry, Kayseri Education and Research Hospital, Kayseri, Turkey; [c]Department of Nuclear Medicine, Erciyes University School of Medicine, Kayseri, Turkey

ABSTRACT

Objective: Childhood maltreatment leads to neuroendocrine changes, which may be associated with an increased vulnerability for psychopathology, such as depression and anxiety in later life. This study aimed to investigate the relationship between childhood maltreatment and orexin A levels in patients with depression and anxiety. The study consisted of 27 female outpatients who presented with depressive and/or anxiety symptoms, and 27 healthy female controls. Childhood trauma history was assessed using the childhood trauma questionnaire (CTQ-28) in patients and controls. Serum levels of orexin and cortisol were measured in all subjects. There were positive correlations between serum orexin levels and CTQ total score and between orexin levels and some CTQ subscale scores, such as physical and emotional neglect, in patients. Orexin levels in patients with a positive history of physical and emotional neglect were higher than those in patients with a negative history of them. In the controls, there was a positive correlation between emotional neglect score and serum orexin level. There were no differences in serum levels of orexin and cortisol between patients and controls. Orexin levels may be associated with childhood maltreatment per se, rather than psychopathology, such as depression or anxiety.

ARTICLE HISTORY
Received 14 July 2015
Revised 18 December 2015
Published online
6 April 2016

KEYWORDS
Depression; anxiety; orexin; childhood maltreatment

Introduction

Orexin A and B were originally named "hypocretins" and were first isolated from the rat hypothalamus (de Lecea et al., 1998; Sakurai et al., 1998). Orexins act via two receptors, called orexin type 1 (OX1) and type 2 (OX2) receptors, that are expressed in the hypothalamic paraventricular nucleus, median eminence, pituitary corticotropes, and adrenal gland (Spinazzi, Andreis, Rossi, & Nussdorfer, 2006). Orexin A has higher liposolubility than orexin B. For this reason, orexin A can rapidly cross the blood–brain barrier by simple diffusion while orexin B cannot. Moreover, the blood concentrations of orexin A are markedly higher than those of orexin B, because orexin B is rapidly metabolized in the blood (Kastin & Akerstrom, 1999). Recently, it has been reported that peripheral concentrations of orexin A reflect central concentrations of orexin A in healthy subject (Strawn et al., 2010).

The functions of orexins are the regulation of sleep/wakefulness and energy homeostasis, the modulation of autonomic functions, the reward system and emotion, and the regulation of hypothalamic–pituitary–adrenal (HPA) axis activity (Kagerer & Johren, 2010; Sakurai, 2005; Sakurai & Mieda, 2011; Spinazzi et al., 2006). There is a reciprocal interaction between orexins and HPA axis activity. Present evidence has indicated that orexins, especially orexin A, may enhance glucocorticoid secretion (Kagerer & Johren, 2010; Spinazzi et al., 2006). On the other hand, orexin activity is also regulated by the HPA axis (Jalewa, Wong-Lin, McGinnity, Prasad, & Holscher, 2014). Most preclinical studies have demonstrated that acute stress increases activation of orexin neurons (Jalewa et al., 2014; Mikrouli, Wortwein, Soylu, Mathe, & Petersen, 2011). However, the role of orexins in chronic stress is still unclear. Both hypoactivity and hyperactivity of orexins have been found to be associated with depression (Nollet & Leman, 2013).

Recent studies have focused on the role of orexins in the adaptive response to repeated stress. Orexin activity on the posterior paraventricular thalamic nucleus has been shown to play a key role in the development of facilitated HPA response, particularly the adaptation to novel stress after repeated stress (Heydendael et al., 2011). Interestingly, recent results have revealed that orexin neurons undergo experience-dependent synaptic plasticity resulting from adaptive changes in response to various physiological, psychological, and environmental stimuli (Gao & Wang, 2010).

CONTACT Saliha Ozsoy sozsoy@erciyes.edu.tr Department of Psychiatry, Erciyes University School of Medicine, 38039 Kayseri, Turkey
© 2016 Informa UK Limited, trading as Taylor & Francis Group

Early life stresses (ELS), such as childhood maltreatment (abuse and neglect) may lead to neuroendocrine changes and structural and functional brain differences, which are considered to be responsible for increased vulnerability for psychopathology, such as depression and anxiety disorders in later life (McCrory, De Brito, & Viding, 2012; Teicher & Samson, 2013). Childhood trauma has been mostly associated with atypical patterns of responsivity in the HPA axis (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Increased or decreased HPA axis responses to challenge tests have been reported in the adults exposed to childhood trauma (Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Klaassens et al., 2009). These neurobiological changes in the stress response system may be the result of an adaptation to ELS and may also affect the orexin system. Therefore, the relationship between childhood maltreatment and the orexin system may be an interesting subject worth investigating. A few preclinical studies have investigated the effect of ELS on orexin activity. One of them found increased hypothalamic corticotrophin releasing hormone (CRH) and orexin A, and frontal cortical OX1 receptors in adult rats neonatally subjected to maternal deprivation (Feng, Vurbic, Wu, & Strohl, 2007). James et al. (2014) demonstrated that restraint stress stimulated Fos-protein expression in the orexin cells in adult rats, but orexin function in ELS-exposed animals was lower than in non-ELS controls (James et al., 2014).

The aim of this study was to investigate the relationship between childhood abuse and neglect and orexin levels in patients with depression and anxiety. Considering the existing evidence in preclinical and clinical studies, we hypothesized that childhood maltreatment may affect the orexin system as a part of the adaptation of the stress system. Thus, we measured serum orexin and cortisol levels and investigated their relation to childhood abuse and neglect. In addition, orexin levels could be associated with psychopathology itself. Therefore, we investigated orexin levels in patients with depression and anxiety.

Methods and materials

Subjects

Twenty-seven female outpatients (mean age ± SD: 32.03 ± 9.69, age range: 25–49) with depressive and anxiety symptoms were recruited for the study. The patients were diagnosed with major depressive disorder (n = 5), generalized anxiety disorder (n = 4), adjustment disorder with depressive symptoms (n = 9), and adjustment disorder with anxiety (n = 9), according to the DSM-IV criteria via clinical interviews. The patients had been undergoing antidepressant drug (venlafaxine, fluoxetine, paroxetine, or sertraline) treatment in standard antidepressant doses for 6–10 weeks.

Twenty-seven physically and mentally healthy women (mean age ± SD: 31.50 ± 7.30, age range: 25–49) who were recruited from volunteers and hospital staff participated in the study as controls.

The exclusion criteria were as follows: any comorbid DSM-IV disorder especially psychotic disorder, bipolar disorder, eating disorder, sleep disorder, and alcohol–drug use disorder (except smoking) for patients; any psychiatric disorder (including sleep and eating disorders) for controls; medical illness (e.g., metabolic and endocrine) or use of hormonal medication for all subjects. All subjects were included in the study after evaluation of history, clinical examination, and their laboratory test results, such as routine hematological tests. The subjects were all in the premenopausal period. None of them were using oral contraceptives.

The study was approved by the local Ethics Committee of Erciyes University. Written informed consent was obtained from all patients and controls after the study had been fully explained to them.

Procedure

The severity of clinical symptomatology was assessed using the Hamilton depression rating scale (HAM-D) for depression and the Hamilton anxiety rating scale (HAM-A) for anxiety. The patients were responders to the treatment, which was assessed by a decrease of more than 50% in depression or anxiety scales.

Childhood trauma history was measured using the childhood trauma questionnaire (CTQ-28) (Bernstein et al., 1994), which is a 28 item questionnaire assessing experiences of childhood abuse and neglect based on a Likert rating scale. The CTQ-28 total score consists of the subscales of physical and emotional abuse, physical and emotional neglect, and sexual abuse. Positivity for maltreatment was defined according to cut-off scores of the Turkish version of the CTQ-28, which were more than 5 for sexual and physical abuse, 7 for physical neglect and emotional abuse, and 12 for emotional neglect (Şar, Öztürk, & İkikardeş, 2012).

Serum levels of orexin and cortisol were measured in all subjects. Blood samples for orexin and cortisol measurement were taken in the morning after an overnight fast. Separated serum was stored at −70°C until analyzed.

Serum orexin A levels were determined with a radioimmunoassay (RIA) kit (Phoenix Pharmaceuticals, Inc., USA) according to the manufacturer's instructions. The measurement range was 10–1280 pg/ml. Serum cortisol levels were

analyzed with a radioimmunoassay kit (Immunotech s.r.o., Czech Republic). The coefficients of variation were 5.8% for intra-assay, and 9.2% for inter-assay. The measurement range was 5 to approximately 2000 nmol.

Statistical analysis

The distributions of all variables were checked with the Shapiro–Wilk test. The significance of differences between the demographic and clinical characteristics of the patients and controls was assessed with the Mann–Whitney *U*-test because of skewed distribution of the values. The hormone levels of the patients and controls were compared with the independent samples *t*-test for orexin and the Mann–Whitney *U*-test for cortisol levels. To control the confounding effects of BMI and age, the multivariate-ANCOVA test was also performed for comparison of hormone levels by taking BMI and age as covariates. The Mann–Whitney *U*-test was used for the analyses of subgroups, according to history of childhood maltreatment because of the small sample size. The Spearman correlation test was performed to investigate the relationships among hormone levels and clinical and demographical variables in the patients and controls separately. To investigate the correlation for CTQ scores and hormones, the partial correlation test was used by controlling education level and BMI.

Results

The patients and controls did not differ significantly in respect of age. The mean of the body mass indexes of the patients was higher than that of the controls. Education duration was lower in the patients than in the controls. The patients' scores for the HAM-D and HAM-A were higher than those of the controls. The CTQ scores of subscales such as physical abuse and emotional neglect and its total scores were also higher than those of the controls (Table 1).

There were no differences in the serum levels of orexin and cortisol between the patients and controls. Adjusted means of orexin and cortisol levels were also compared by controlling the effect of BMI and age with ANCOVA. The result, namely no difference between patients and controls with regard to orexin and cortisol levels, remained the same (Table 2).

There were positive correlations between CTQ total score and some subscale scores, such as physical neglect and emotional neglect and serum orexin levels in patients. The result was still similar, even after controlling the confounding effect of education level and BMI with the partial correlation test. In the controls, there was a positive correlation between the emotional neglect score and serum orexin level. When the effect of education level and BMI was controlled, the correlation was also remained for controls (Table 3).

Correlation tests were also performed to the patient and control groups together because no difference in orexin levels was shown between them. There were positive correlations between CTQ total score and the subscale scores including physical and emotional neglect, and serum orexin levels in all subjects ($r = 0.432$ $p = 0.001$, $r = 0.421$ $p = 0.002$, $r = 0.503$ $p < 0.001$, respectively; $r = 0.359$ $p = 0.009$, $r = 0.374$ $p = 0.006$, $r = 0.454$ $p = 0.001$, respectively, by controlling education level and BMI).

The patients were divided into two subgroups according to the positivity of maltreatment by using cut-off values of the Turkish version of the CTQ-28.

Table 1. Demographic and clinical characteristics of the subjects.

	Patients $n = 27$ Mean ± SD	Controls $n = 27$ Mean ± SD	Comparisons
Age	34.19 ± 7.27	32.78 ± 6.92	$Z = 0.694$ $p = 0.487$
Education levels (year)	8.92 ± 4.08[a]	14.88 ± 3.34	$Z = 4.927$ $p < 0.001$
BMI	26.73 ± 4.94[b]	23.13 ± 3.40	$Z = 3.080$ $p = 0.002$
HAM-D	10.74 ± 5.95[b]	1.26 ± 1.83	$Z = 5.722$ $p < 0.001$
HAM-A	17.04 ± 11.77[b]	3.18 ± 1.75	$Z = 5.545$ $p < 0.001$
CTQ (emotional abuse)	7.37 ± 3.21	5.96 ± 1.22	$Z = 1.280$ $p = 0.200$
CTQ (physical abuse)	5.37 ± 0.79[b]	5 ± 0	$Z = 2.569$ $p = 0.010$
CTQ (physical neglect)	6.70 ± 2.12	5.85 ± 1.23	$Z = 1.603$ $p = 0.109$
CTQ (emotional neglect)	11.04 ± 5.15[b]	6.81 ± 2.07	$Z = 3.092$ $p = 0.002$
CTQ (sexual abuse)	6.11 ± 3.04	5.07 ± 0.26	$Z = 1.349$ $p = 0.177$
CTQ (total)	36.59 ± 10.47[b]	28.70 ± 3.83	$Z = 2.409$ $p = 0.016$

BMI, body mass index, HAM-D, Hamilton depression rating scale, HAM-A, Hamilton anxiety rating scale, CTQ, childhood trauma questionnaire, SD, standard deviation.
[a]Lower than those of the controls.
[b]Higher than those of the controls.

Table 2. Serum orexin and cortisol levels of the patients and controls.

	Patients $n = 27$	Controls $n = 27$	Comparisons
Orexin (pg/ml) (mean ± SD)	14.44 ± 3.90	13.00 ± 4.45	$t = 1.270$ $p = 0.210$
Orexin (adjusted mean ± SE)	14.55 ± 0.86	12.89 ± 0.86	$F = 1.705$ $p = 0.198$
Cortisol (μg/dl) (mean ± SD)	9.49 ± 4.27	11.73 ± 6.46	$Z = 1.531$ $p = 0.126$
Cortisol (adjusted mean ± SE)	9.46 ± 1.12	11.77 ± 1.12	$F = 1.940$ $p = 0.170$

SD, standard deviation. SE, standard error.

Table 3. Correlations between CTQ scores and orexin A level in the patients and controls.

	Orexin levels of the patients $n = 27$		Orexin levels of the controls $n = 27$	
	Without controlling education level and BMI	By controlling education level and BMI	Without controlling education level and BMI	By controlling education level and BMI
CTQ (emotional abuse)	$r = 0.376$	$r = 0.229$	$r = 0.011$	$r = 0.044$
	$p = 0.053$	$p = 0.271$	$p = 0.956$	$p = 0.833$
CTQ (physical abuse)	$r = 0.111$	$r = 0.100$	–	–
	$p = 0.582$	$p = 0.633$		
CTQ (physical neglect)	$r = 0.540$	$r = 0.412$	$r = 0.200$	$r = 0.366$
	$p = 0.004$	$p = 0.041$	$p = 0.316$	$p = 0.072$
CTQ (emotional neglect)	$r = 0.582$	$r = 0.555$	$r = 0.416$	$r = 0.446$
	$p = 0.001$	$p = 0.004$	$p = 0.031$	$p = 0.026$
CTQ (sexual abuse)	$r = 0.029$	$r = -0.001$	$r = 0.211$	$r = 0.212$
	$p = 0.886$	$p = 0.997$	$p = 0.291$	$p = 0.309$
CTQ (total)	$r = 0.449$	$r = 0.430$	$r = 0.315$	$r = 0.390$
	$p = 0.019$	$p = 0.032$	$p = 0.109$	$p = 0.054$

BMI, body mass index, CTQ, childhood trauma questionnaire.

The maltreatment positive and negative groups were compared in respect to orexin and cortisol levels for each subscale in the patients. Serum levels of orexin in the patients with a positive history of physical neglect (mean ± SD: 17.25 ± 2.31, $n = 8$) and emotional neglect (mean ± SD: 17.54 ± 2.42, $n = 11$) were higher than those in the patients with a negative history of physical neglect (mean ± SD: 13.26 ± 3.85, $n = 19$) and emotional neglect (mean ± SD: 12.31 ± 3.24, $n = 16$) ($Z = 2.513$, $p = 0.012$; $Z = 3.527$, $p < 0.001$; respectively).

Discussion

The main result of this study is that a significant relationship was found between severity of childhood maltreatment, especially physical and emotional neglect, and serum orexin levels in women with depression and anxiety. Similarly, the serum levels of orexin in patients with a positive history of physical and emotional neglect were higher than those in patients with a negative history of physical and emotional neglect. In sum, serum orexin levels were increased with high scores of history of childhood maltreatment in the patients. However, a positive correlation between orexin levels and maltreatment was also found in the healthy women for emotional neglect. In addition, we found no difference between the orexin levels of the patients and controls and no correlation between orexin levels and symptom severity in this study. Therefore, it may be proposed that orexin levels are associated with childhood maltreatment per se, rather than psychopathology, such as depression or anxiety. Previous human studies have also reported contradictory results about orexin levels in chronic stress situations, such as depression. The clinical literature indicates that depression may be associated with decreased or increased activity of the orexin system (Brundin, Bjorkqvist, Petersen, & Traskman-Bendz, 2007; Salomon et al., 2003). A recent study showed no difference between cerebrospinal fluid orexin A levels in five depressive patients and in healthy controls (Schmidt et al., 2010), which is similar to our result. As a limitation, our study population did not consist of patients with depression or anxiety alone. Therefore, the heterogeneity of our study population may make assessment difficult about relationship between psychopathology and orexin.

The most important result of this study is positive correlation between orexin A levels and scores of history of childhood maltreatment, especially neglect, in the patients and controls. Serum orexin A levels seems to be related to childhood neglect but not with abuse. Childhood neglect might have been more affected orexin A directly or indirectly. The relationship between orexin and childhood neglect may result from the impacts of childhood maltreatment on the HPA axis. Previous studies, which investigated the effects of childhood maltreatment on the HPA axis revealed that childhood maltreatment is associated with impairment in HPA axis response in adults even without psychopathology (Carpenter et al., 2009; Klaassens et al., 2009). Stress is known to increase CRH centrally and cortisol levels peripherally (Bao, Meynen, & Swaab, 2008). Childhood trauma has some impacts on HPA axis activity, such as an increase in corticotrophin releasing factor (CRF) activity. CRF and orexin interactively regulate responses to stress. CRF stimulates the release of orexins (Winsky-Sommerer et al., 2004). Childhood maltreatment may affect orexin activity via the HPA axis. In order to be able to show the association between the HPA axis and orexin, we measured cortisol level in this study. Nevertheless, there was no correlation between levels of cortisol and orexin. Of course, the measurement of basal cortisol level alone was not enough to assess HPA axis activity. If we had performed some challenge

tests, it would have been possible to show this association.

The direct effect of childhood maltreatment on the orexin system may also be another cause of the relationship between orexin and childhood neglect. Orexin activity is reported to be induced under stress-like conditions, which are high-arousal conditions associated with elevated motivation and/or the need for action (Berridge, España, & Vittoz, 2010). Furthermore, orexin mRNA in the lateral hypothalamic area has been shown to be upregulated in response to acute restraint stress (Reyes, Walker, DeCino, Hogenesch, & Sawchenko, 2003). In our study, the increase in orexin levels associated with childhood maltreatment may be considered to be a result of adaptive process in response to repeated stress. Indeed, recent studies have demonstrated that the orexin system is highly plastic and is easily modified by environmental events (Gao & Wang, 2010; James et al., 2014). The role of orexins in the adaptive response to stress is obvious. Accumulated data have provided evidence of early environmental programming of neural systems (Meaney et al., 1996). The orexin system is one of the primary targets of this programming. The changes in the number and/or activity of orexin neurons as a consequence of ELS may play a role in response to later life stress.

Major limitation of the present study has seemed that we measured serum orexin levels which may lessen the impact of our findings. However, recent data demonstrated that plasma orexin A concentrations were highly correlated with CSF orexin A concentrations (Strawn et al., 2010). Low levels of orexin A were found in serial CSF and plasma samples of patients with post-traumatic stress disorder (Strawn et al., 2010). Reduced and undetectable levels of CSF orexin A have been demonstrated in patients with narcolepsy, in which CFS orexin can be used as a biological marker (Nishino, Ripley, Overeem, Lammers, & Mignot, 2000). Low levels of orexin A in plasma were also reported in patients with narcolepsy and were also suggested to serve as a biological marker for narcolepsy (Higuchi et al., 2002).

In the present study, childhood trauma history was reported by the patients themselves, which may have resulted in a recall bias. We did not perform a justification method for childhood trauma history as a limitation. The fact that the patients were under antidepressant treatment may also be a limitation. However, we preferred to apply the CTQ in responding patients, because depressive mood may affect retrospective evaluation for history of childhood maltreatment. Nevertheless, medication might be a confounding factor as a limitation. The mean of the BMI of the patients was higher than that of the controls. This could have confounded the data. However, we tried to control confounding factors by analyzing hormone values taking as covariates. Finally, another important limitation is the relatively small sample size, especially when the sub-groups were analyzed.

In conclusion, orexin activity seems to be associated with childhood trauma. An increase in orexin levels associated with childhood maltreatment may be the result of repeated stress. On the other hand, higher orexin levels associated with childhood maltreatment may be an attempt to compensate or neutralize the negative effects of early trauma. Indeed, a study by Flores et al. (2014) proposed a key role for orexins in the extinction of aversive memories and suggested that orexin receptor-1 blockade could represent a novel therapeutic target for the treatment of disorders such as post-traumatic stress disorder (Flores et al., 2014). The result of our study, namely the existence of a relationship between childhood trauma and orexin, may provide evidence for a novel idea like this. Thus, we may speculate that orexinergic activity may be a novel therapeutic target for protection from the harmful effects of childhood trauma.

Acknowledgements

The technical assistance provided by Mrs. Husniye Tayyar is acknowledged.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Research Fund of Erciyes University: [grant number: TTU-2012-4185].

References

Bao, A.-M., Meynen, G., & Swaab, D. F. (2008). The stress system in depression and neurodegeneration: Focus on the human hypothalamus. *Brain Research Reviews*, *57*(2), 531–553. doi:10.1016/j.brainresrev.2007.04.005

Bernstein, D. P., Fink, L., Handelsman, L., Foote, J., Lovejoy, M., Wenzel, K., & Ruggiero, J. (1994). Initial reliability and validity of a new retrospective measure of child abuse and neglect. *The American Journal of Psychiatry*, *151*(8), 1132–1136. doi:10.1176/ajp.151.8.1132

Berridge, C. W., España, R. A., & Vittoz, N. M. (2010). Hypocretin/orexin in arousal and stress. *Brain Research*, *1314*, 91–102. doi:10.1016/j.brainres.2009.09.019

Brundin, L., Bjorkqvist, M., Petersen, A., & Traskman-Bendz, L. (2007). Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. *European Neuropsychopharmacology: the Journal of the European College of Neuropsychopharmacology*, *17*(9), 573–579. doi:10.1016/j.euroneuro.2007.01.005

Carpenter, L. L., Tyrka, A. R., Ross, N. S., Khoury, L., Anderson, G. M., & Price, L. H. (2009). Effect of childhood emotional abuse and age on cortisol responsivity in adulthood. *Biological Psychiatry*, *66*(1), 69–75. doi:10.1016/j.biopsych.2009.02.030

de Lecea, L., Kilduff, T. S., Peyron, C., Gao, X., Foye, P. E., Danielson, P. E., & Sutcliffe, J. G. (1998). The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(1), 322–327. doi:10.1073/pnas.95.1.322

Feng, P., Vurbic, D., Wu, Z., & Strohl, K. P. (2007). Brain orexins and wake regulation in rats exposed to maternal deprivation. *Brain Research*, *1154*, 163–172. doi:10.1016/j.brainres.2007.03.077

Flores, A., Valls-Comamala, V., Costa, G., Saravia, R., Maldonado, R., & Berrendero, F. (2014). The hypocretin/orexin system mediates the extinction of fear memories. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *39*(12), 2732–2741. doi:10.1038/npp.2014.146

Gao, X.-B., & Wang, A. H. (2010). Experience-dependent plasticity in hypocretin/orexin neurones: Re-setting arousal threshold. *Acta Physiologica*, *198*(3), 251–262. doi:10.1111/j.1748-1716.2009.02047.x

Heim, C., Mletzko, T., Purselle, D., Musselman, D. L., & Nemeroff, C. B. (2008). The dexamethasone/corticotropin-releasing factor test in men with major depression: Role of childhood trauma. *Biological Psychiatry*, *63*(4), 398–405. doi:10.1016/j.biopsych.2007.07.002

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: İnsights from HPA axis studies in humans. *Psychoneuroendocrinology*, *33*(6), 693–710. doi:10.1016/j.psyneuen.2008.03.008

Heydendael, W., Sharma, K., Iyer, V., Luz, S., Piel, D., Beck, S., & Bhatnagar, S. (2011). Orexins/hypocretins act in the posterior paraventricular thalamic nucleus during repeated stress to regulate facilitation to novel stress. *Endocrinology*, *152*(12), 4738–4752. doi:10.1210/en.2011-1652

Higuchi, S., Usui, A., Murasaki, M., Matsushita, S., Nishioka, N., Yoshino, A., & Sakurai, T. (2002). Plasma orexin-A is lower in patients with narcolepsy. *Neuroscience Letters*, *318*(2), 61–64. doi:10.1016/S0304-3940(01)02476-4

Jalewa, J., Wong-Lin, K., McGinnity, T. M., Prasad, G., & Holscher, C. (2014). Increased number of orexin/hypocretin neurons with high and prolonged external stress-induced depression. *Behavioural Brain Research*, *272*, 196–204. doi:10.1016/j.bbr.2014.05.030

James, M. H., Campbell, E. J., Walker, F. R., Smith, D. W., Richardson, H. N., Hodgson, D. M., & Dayas, C. V. (2014). Exercise reverses the effects of early life stress on orexin cell reactivity in male but not female rats. *Frontiers in Behavioral Neuroscience*, *8*, 244. doi:10.3389/fnbeh.2014.00244

Kagerer, S. M., & Johren, O. (2010). Interactions of orexins/hypocretins with adrenocortical functions. *Acta Physiologica*, *198*(3), 361–371. doi:10.1111/j.1748-1716.2009.02034.x

Kastin, A. J., & Akerstrom, V. (1999). Orexin A but not orexin B rapidly enters brain from blood by simple diffusion. *The Journal of Pharmacology and Experimental Therapeutics*, *289*(1), 219–223. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10087007

Klaassens, E. R., Van Noorden, M. S., Giltay, E. J., van Pelt, J., van Veen, T., & Zitman, F. G. (2009). Effects of childhood trauma on HPA-axis reactivity in women free of lifetime psychopathology. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*(5), 889–894. doi:10.1016/j.pnpbp.2009.04.011

McCrory, E., De Brito, S. A., & Viding, E. (2012). The link between child abuse and psychopathology: A review of neurobiological and genetic research. *Journal of the Royal Society of Medicine*, *105*(4), 151–156. doi:10.1258/jrsm.2011.110222

Meaney, M. J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., & Plotsky, P. M. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: İmplications for adrenocortical responses to stress. *Developmental Neuroscience*, *18*(12), 49–72. doi:10.1159/000111395

Mikrouli, E., Wortwein, G., Soylu, R., Mathe, A. A., & Petersen, A. (2011). Increased numbers of orexin/hypocretin neurons in a genetic rat depression model. *Neuropeptides*, *45*(6), 401–406. doi:10.1016/j.npep.2011.07.010

Nishino, S., Ripley, B., Overeem, S., Lammers, G. J., & Mignot, E. (2000). Hypocretin (orexin) deficiency in human narcolepsy. *The Lancet*, *355*(9197), 39–40. doi:10.1016/S0140-6736(99)05582-8

Nollet, M., & Leman, S. (2013). Role of orexin in the pathophysiology of depression: Potential for pharmacological intervention. *CNS Drugs*, *27*(6), 411–422. doi:10.1007/s40263-013-0064-z

Reyes, T. M., Walker, J. R., DeCino, C., Hogenesch, J. B., & Sawchenko, P. E. (2003). Categorically distinct acute stressors elicit dissimilar transcriptional profiles in the paraventricular nucleus of the hypothalamus. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *23*(13), 5607–5616. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12843263

Sakurai, T. (2005). Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. *Sleep Medicine Reviews*, *9*(4), 231–241. doi:10.1016/j.smrv.2004.07.007

Sakurai, T., Amemiya, A., Ishii, M., Matsuzaki, I., Chemelli, R. M., Tanaka, H., & Yanagisawa, M. (1998). Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*, *92*(4), 573–585. doi:10.1016/S0092-8674(00)80949-6

Sakurai, T., & Mieda, M. (2011). Connectomics of orexin-producing neurons: İnterface of systems of emotion, energy homeostasis and arousal. *Trends in Pharmacological Sciences*, *32*(8), 451–462. doi:10.1016/j.tips.2011.03.007

Salomon, R. M., Ripley, B., Kennedy, J. S., Johnson, B., Schmidt, D., Zeitzer, J. M., & Mignot, E. (2003). Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. *Biological Psychiatry*, *54*(2), 96–104. doi:10.1016/S0006-3223(02)01740-7

Şar, V., Öztürk, E., & İkikardeş, E. (2012). Validity and reliability of the turkish version of childhood trauma questionnaire.

Turkiye Klinikleri Journal of Medical Sciences, *32*(4), 1054–1063. doi:10.5336/medsci.2011-26947

Schmidt, F. M., Brugel, M., Kratzsch, J., Strauss, M., Sander, C., Baum, P., & Schonknecht, P. (2010). Cerebrospinal fluid hypocretin-1 (orexin A) levels in mania compared to unipolar depression and healthy controls. *Neuroscience Letters*, *483*(1), 20–22. doi:10.1016/j.neulet.2010.07.038

Spinazzi, R., Andreis, P. G., Rossi, G. P., & Nussdorfer, G. G. (2006). Orexins in the regulation of the hypothalamic-pituitary-adrenal axis. *Pharmacological Reviews*, *58*(1), 46–57. doi:10.1124/pr.58.1.4

Strawn, J. R., Pyne-Geithman, G. J., Ekhator, N. N., Horn, P. S., Uhde, T. W., Shutter, L. A., & Geracioti, T. D., Jr. (2010). Low cerebrospinal fluid and plasma orexin-A (hypocretin-1) concentrations in combat-related posttraumatic stress disorder. *Psychoneuroendocrinology*, *35*(7), 1001–1007. doi:10.1016/j.psyneuen.2010.01.001

Teicher, M. H., & Samson, J. A. (2013). Childhood maltreatment and psychopathology: A case for ecophenotypic variants as clinically and neurobiologically distinct subtypes. *The American Journal of Psychiatry*, *170*(10), 1114–1133. doi:10.1176/appi.ajp.2013.12070957

Winsky-Sommerer, R., Yamanaka, A., Diano, S., Borok, E., Roberts, A. J., Sakurai, T., & de Lecea, L. (2004). Interaction between the corticotropin-releasing factor system and hypocretins (orexins): A novel circuit mediating stress response. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, *24*(50), 11439–11448. doi:10.1523/JNEUROSCI.3459-04