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Editorial OMICS International

Orexinergic System Dysregulation in Depression

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Editorial

Depression is an affective disorder characterized, in particular in its more severe form, i.e., major depressive disorder (MDD), by persistent symptoms of unpleasant (dysphoric) mood, inability to experience pleasure (anhedonia), and a generalized loss of interest in most or all normal activities [1]. Depression is often associated with physiological and cognitive symptoms. Physiological symptoms include sleep disorders, changes in appetite, tiredness and lack of energy; cognitive symptoms consist of trouble thinking, concentrating, remembering things, and recurrent thoughts of death and suicidal thoughts. Several brain regions regulating emotion and cognition have been implicated in depression, such as the prefrontal cortex, the cingulate cortex, the nucleus accumbens, the amygdala, the hippocampus and the hypothalamus [2]. A variety of factors seem to be involved in the pathophysiology of depression, such as the occurrence of psychosocial stressful events, changes in the function and effect of monoamines and abnormal functioning of the hypothalamic–pituitary–adrenal (HPA) axis. The activation of the HPA axis is common in depressed patients. The excessive secretion of cortisol damages mature neurons and suppresses normal neurogenesis, leading to a reduction of hippocampal volume. It is important to note that the hippocampus inhibits the hypothalamic corticotrophin releasing factor (CRH) secretion. Thus, the damage to the hippocampus may lead to a vicious cycle in which the loss of inhibitory control of CRH secretion would lead to greater cortisol release, producing additional hippocampal atrophy [3].

Recently, several experimental observations have led to propose the involvement of orexinergic system in pathophysiology of depression. The orexinergic system regulates functions that are disturbed in depressive states such as sleep, feeding behavior, and reward system and stress response. Both hypoactivity and hyperactivity of orexinergic system have been found to be associated with depression and could reflect the heterogeneity of depression [4,5]. The orexin-A (OX-A) and orexin-B (OX-B) (hypocretin-1 and hypocretin-2) are neuropeptides synthesized by a cluster of neurons in the lateral hypothalamus. Orexins selectively act on two G protein-coupled receptors: the orexin/hypocretin 1 receptor (Ox1R/HcrtR1), which has higher affinity to OX-A, and the orexin/hypocretin 2 receptor (Ox2R/HcrtR2), which has equal affinity to both OX-A and OX-B [6,7]. Orexinergic neurons receive a variety of signals related to environmental, physiological and emotional stimuli, and project broadly to the entire CNS. Orexinergic projections are involved in regulating wakefulness and arousal, motivation and emotions, feeding behavior and motor and autonomic functions [8-14].

Salomon et al. [15] found that cerebrospinal fluid (CSF) OX-A levels in depressive subjects trended to be higher than in control, and varied less than in controls across the diurnal cycle. Surprisingly, OX-A levels were lowest at midday, although the orexin is a hypothetically wake-promoting peptide. It is probable that the orexin levels are lowest at midday since there is a long delay between OX-A release and its appearance in CSF [16]. However, others studies found a decrease of CFS OX-A levels in depression. Brundin et al. [17,18] explored the CSF level of OX-A in depressed patients admitted to hospital shortly after a suicide attempt. Brundin L et al. [17] found significant and negative correlations between CSF-orexin and two psychiatric symptoms of the Comprehensive Psychopathological Rating Scale (lassitude and slowness of movement), and the ratings of global illness, as observed by a psychiatrist. Interestingly, Brundin et al. [18] observed that orexin correlated significantly with CSF levels of CRF, suggesting that orexin and the HPA-axis hormones interact in humans. This was supported by the observation that intracerebroventricular (i.c.v.) infusion of OX-A activates CRF neurons of the paraventricular nucleus of the hypothalamus [19] and elevates HPA hormones [20]. Although the majority of studies showed an activation of the HPA-axis in depression [21], other researches reported a reduction of CRF in suicidal patients with MDD [22,23]. Brundin et al. [18] proposed that in severe and chronic depression the HPA-axis becomes exhausted and the CRH secretion reduced.

Experimental observations supporting the hypothesis of an orexinergic system dysregulation in depression were also obtained using animal models. Flinders Sensitive Line (FSL) rats [24] are considered as a genetic animal model of depression. These rats exhibit an increase of immobility in the forced swim test (FST), a commonly used measure of depressive behavior, and display characteristics similar to those of depressed patients including lower body weight, decreased appetite and reduced REM sleep latency. Importantly, FSL rats showed a higher number of orexin neurons in the hypothalamus than Flinders Resistant Line rats [24]. Negative effects related to overactivation of orexin neurons were observed by Nollet et al. [25,26]. The authors [25] exposed mice to the unpredictable chronic mild stress (UCMS), a rodent model of depression. UCMS induced orexin neurons overactivation, HPA axis dysregulation and the suppression of cell proliferation and neurogenesis in the hippocampus. Some of these effects were reversed by the administration of almorexant, a dual orexin receptor antagonist. Almorexant induced antidepressant-like effect preventing the HPA axis dysregulation, but it did not reversed the UCMS-induced hippocampal cell proliferation and neurogenesis suppression [26]. However, these observations were at odds with studies that used a different genetic animal model of depression, the Wistar-Kyoto (WKY) rats. WKY rats exhibit depressive characteristics and patterns of sleep disruption similar to that observed in depressed human patients. WKY rats had fewer (about 18%) and smaller (about 15%) OX-A neurons in the hypothalamus compared to control Wistar rats [27]. These observations [27] were in agreement with those reported by Taheri et al. [28] who found a decrease of about 22% in hypothalamic prepro-orexin mRNA in WKY rats. Some studies have investigated the links

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between orexins, depression and hippocampal neurogenesis. Arendt et al. [29] found that mice displaying more severe depressive behavior in FST had lower hippocampal expression of OX-A. Furthermore, the i.c.v. administration of OX-A led to a significant reduction in animal immobility in the FST, without changing the corticosterone blood level, and an increase in the number of cells in the dentate gyrus [30]. Ito et al. [30] suggested that the enhancement of cell proliferation in the dentate gyrus by OX-A might have an antidepressive-like effect. The treatment with the OXR1 antagonist SB-334867 blocked both the OX-A-induced decrease in the FST immobility and the increase in the number of cells in the dentate gyrus.

Experimental evidence suggest that physical exercise has beneficial effects on mood regulation and improves cognition [31,32]. These beneficial effects are associated with morphological and functional changes of brain regions involved in mood regulation and cognition such as prefrontal region [33-36] and the hippocampus [37]. Interestingly, these regions are often reported to deteriorate with aging [38] and be severely affected in Alzheimer's disease [39,40]. The exercise-induced beneficial effects on hippocampus would depend on more factors including the enhancement of vascularisation, the upregulation of neurotrophic factors and, possibly, an increase of OX-A levels. An increase of OX-A levels with physical exercise has been reported in rats [41], dogs [42], cats [43], and humans [44].

Taken together, the studies reported suggest an involvement of orexinergic system in depressive disorders. However, the exact nature of the orexinergic dysfunction is not yet fully understood. Human and animal studies led to conflicting results, being depressive state associated with either hypoactivity or hyperactivity of the orexinergic system. However, most studies focused on a general diagnosis of depression. They did not distinguish the role of orexin system in different subtypes of depression that might depend on different pathophysiological mechanisms. Further investigations are necessary to clarify the mechanisms linking orexinergic system and depression in animals and humans.

References

1. Keller MC, Neale MC, Kendler KS (2007) Association of different adverse life events with distinct patterns of depressive symptoms. Am J Psychiatry 164: 1521–1529.
2. Krishnan V, Nestler EJ (2008) The molecular neurobiology of depression. Nature 455: 894-902.
3. Hyman SE, Cohen JD (2013) Disorders of mood and anxiety. In: Kandel ER, Schwartz JH, Jessell TM, Siegelbaum SA, Hudspeth AJ, et al. (eds.) Principles of Neural Science, Fifth Editon. McGraw-Hill Companies, Inc., USA.
4. Nollet M, Leman S (2013) Role of orexin in the pathophysiology of depression: potential for pharmacological intervention. CNS Drugs 27: 411-22.
5. Chen Q, Lecea LD, Hu Z, Gao D (2015) The hypocretin/orexin system: an increasingly important role in neuropsychiatry. Med Res Rev 35: 152-197.
6. Scammell TE, Winrow CJ (2011) Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol 51: 243-266.
7. Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, et al. (2001) Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol 435: 6-25.
8. Saper CB, Scammell TE, Lu J (2005) Hypothalamic regulation of sleep and circadian rhythms. Nature 437: 1257-1263.
9. Sakurai T, Mieda M (2011) Connectomics of orexin-producing neurons: interface of systems of emotion, energy homeostasis and arousal. Trends Pharmacol Sci 32: 451-462.
10. Marra L, Cantile M, Scognamiglio G, Perdonà S, Mantia EL, et al. (2013) Deregulation of HOX B13 expression in urinary bladder cancer progression. Curr Med Chem 20: 833-839.
11. Messina G, Monda V, Moscatelli F, Valenzano AA, Monda G, et al. (2015) Role of orexin system in obesity. Biol Med (Aligarh) 7: 248.
12. Messina G, Palmieri F, Monda V, Messina A, Dalia C, et al. (2015) Exercise causes muscle GLUT4 translocation in an insulin-independent manner. Biol Med (Aligarh) 1: 006.
13. Messina G, Viggiano A, Tafuri D, Palmieri F, De Blasio S, et al. (2014) Role of orexin in obese patients in the intensive care unit. J Anesth Clin Res 5: 395.
14. Nattie E, Li A (2012) Respiration and autonomic regulation and orexin. Prog Brain Res 198: 25-46.
15. Salomon RM, Ripley B, Kennedy JS, Johnson B, Schmidt D, et al. (2003) Diurnal variation of cerebrospinal fluid hypocretin-1 (Orexin-A) levels in control and depressed subjects. Biol Psychiatry 54: 96-104.
16. Grady SP, Nishino S, Czeisler CA, Hepner D, Scammell TE (2006) Diurnal variation in CSF orexin-A in healthy male subjects. Sleep 29: 295-297.
17. Brundin L, Petersén A, Björkqvist M, Träskman-Bendz L (2007) Orexin and psychiatric symptoms in suicide attempters. J Affect Disord 100: 259-263.
18. Brundin L, Björkqvist M, Petersén A, Träskman-Bendz L (2007) Reduced orexin levels in the cerebrospinal fluid of suicidal patients with major depressive disorder. Eur Neuropsychopharmacol 17: 573-579.
19. Sakamoto F, Yamada S, Ueta Y (2004) Centrally administered orexin-A activates corticotropin-releasing factor-containing neurons in the hypothalamic paraventricular nucleus and central amygdaloid nucleus of rats: possible involvement of central orexins on stress-activated central CRF neurons. Regul Pept 118: 183-191.
20. Kuru M, Ueta Y, Serino R, Nakazato M, Yamamoto Y, et al. (2000) Centrally administered orexin/hypocretin activates HPA axis in rats. Neuroreport 11: 1977-1980.
21. Varghese FP, Brown ES (2001) The hypothalamic-pituitary-adrenal axis in major depressive disorder: A brief primer for primary care physicians. Prim Care Companion J Clin Psychiatry 3: 151-155.
22. Traskman-Bendz L, Ekman R, Regnell G, Ohman R (1992) HPA related CSF neuropeptides in suicide attempters. Eur Neuropsychopharmacol 2: 99-106.
23. Geracioti Jr TD, Orth DN, Ekhator NN, Blumenkopf B, Loosen PT (1992) Serial cerebrospinal fluid corticotropin-releasing hormone concentrations in healthy and depressed humans. J Clin Endocrinol Metab 74: 1325–1330.
24. Mikrouli E, Wörtwein G, Soylu R, Mathé AA, Petersén Å (2011) Increased numbers of orexin/hypocretin neurons in a genetic rat depression model. Neuropeptides 45: 401-406.
25. Nollet M, Gaillard P, Minier F, Tanti A, Belzung C, et al. (2011) Activation of orexin neurons in dorsomedial/perifornical hypothalamus and antidepressant reversal in a rodent model of depression. Neuropharmacology 61: 336-346.
26. Nollet M, Gaillard P, Tanti A, Girault V, Belzung C, et al. (2012) Neurogenesis-independent antidepressant-like effects on behavior and stress axis response of a dual orexin receptor antagonist in a rodent model of depression. Neuropsychopharmacology 37: 2210-2221.
27. Allard JS, Tizabi Y, Shaffery JP, Trouth CO, Manaye K (2004) Stereological analysis of the hypothalamic hypocretin/orexin neurons in an animal model of depression. Neuropeptides 38: 311-315.
28. Taheri S, Gardiner J, Hafizi S, Murphy K, Dakin C, et al. (2001) Orexin A immunoreactivity and preproorexin mRNA in the brain of Zucker and WKY rats. Neuroreport 12: 459-464.
29. Arendt DH, Ronan PJ, Oliver KD, Callahan LB, Summers TR, et al. (2013) Depressive behavior and activation of the orexin/hypocretin system. Behav Neurosci 127: 86-94.
30. Ito N, Yabe T, Nagai T, Oikawa T, Yamada H, et al. (2009) A possible mechanism underlying an antidepressive-like effect of Kososan, a Kampo medicine, via the hypothalamic orexinergic system in the stress-induced depression-like model mice. Biol Pharm Bull 32: 1716-1722.
31. Blake H, Mo P, Malik S, Thomas S (2009) How effective are physical activity interventions for alleviating depressives ymptoms in older people? A systematic review. Clin Rehabil 23: 873-887.
32. Kvam S, Kleppe CL, Nordhus IH, Hovland A (2016) Exercise as a treatment for depression: A meta-analysis. J Affect Disord 202: 67-86.

33. Roca M, Parr A, Thompson R, Woolgar A, Torralva T, et al. (2010). Executive function and fluid intelligence after frontal lobe lesions. Brain 133: 234-47.

34. Chieffi S, Secchi C, Gentilucci M (2009) Deictic word and gesture production: Their interaction. Behav Brain Res 203: 200-206.

35. Chieffi S, Iachini T, Iavarone A, Messina G, Viggiano A, et al. (2014) Flanker interference effects in a line bisection task. Exp Brain Res 232: 1327-1334.

36. Iavarone A, Patruno M, Galeone F, Chieffi S, Carlomagno S (2007) Brief report: error pattern in an autistic savant calendar calculator. J Autism Dev Disord 37: 775-779.

37. Jeneson A, Squire LR (2011) Working memory, long-term memory, and medial temporal lobe function. Learn Mem 19: 15-25.

38. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, et al. (2006) Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci 61: 1166-1170.

39. Chieffi S, Iavarone A, Viggiano A, Monda M, Carlomagno S (2012) Effect of a visual distractor on line bisection. Exp Brain Res 219: 489-498.

40. Chieffi S, Conson M, Carlomagno S (2004) Movement velocity effects on kinaesthetic localisation of spatial positions. Exp Brain Res 158: 421-426.

41. Martins PJ, D'Almeida V, Pedrazzoli M, Lin L, Mignot E, et al. (2004) Increased hypocretin-1 (orexin-a) levels in cerebrospinal fluid of rats after short-term forced activity. Regul Pept 117: 155-158.

42. Wu MF, John J, Maidment N, Lam HA, Siegel JM (2002) Hypocretin release in normal and narcoleptic dogs after food and sleep deprivation, eating, and movement. Am J Physiol Regul Integr Comp Physiol 283: R1079-1086.

43. Kiyashchenko LI, Mileykovskiy BY, Maidment N, Lam HA, Wu MF, et al. (2002) Release of hypocretin (orexin) during waking and sleep states. J Neurosci 22: 5282-5286.

44. Messina G, Di Bernardo G, Viggiano A, De Luca V, Monda V, et al. (2016) Exercise increases the level of plasma orexin A in humans. J Basic Clin Physiol Pharmacol 27: 611-616.

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