Scientific Research Publishing

World Journal of Neuroscience, 2022, 12, 45-56
https://www.scirp.org/journal/wjns
ISSN Online: 2162-2019
ISSN Print: 2162-2000

Biochemical Changes in the Brain and Metabolism as Risk Factors of Neurological Disorders

Kevin Patrick Barman

SAERA (School of Advanced Education, Research, and Accreditation, and Education), Castellon de la Plana, Spain
Email: kbarman@riohondo.edu

How to cite this paper: Barman, K.P. (2022) Biochemical Changes in the Brain and Metabolism as Risk Factors of Neurological Disorders. *World Journal of Neuroscience*, **12**, 45-56.
https://doi.org/10.4236/wjns.2022.122006

Received: February 16, 2022
Accepted: May 3, 2022
Published: May 6, 2022

Abstract

This paper aims to examine theories that attempt to explain biochemical changes in the brain as well as the metabolism of individuals who experience symptoms and conditions related to neurological disorders like depression. A systematic literature search was performed on NCBI and PubMed. The search included the keywords neurological disorders, monoamine hypothesis, metabolic syndrome, oxytocin receptor, dietary health, and magnesium intake. Twenty-five research articles met the criteria for the literature review of this examination. In particular, this paper will review multiple studies that investigate the monoamine (MAO) hypothesis of depression and metabolic syndrome (MetS) as a risk factor for neurological disorders. While studies that evaluate additional risk factors for neurological disorders, such as autoimmunity and rheumatic diseases, oxytocin receptor (OXTR) DNA methylation in postpartum depression, dietary health in children and their psychological health, and dietary magnesium and cardiovascular disease, will be reviewed as well.

Keywords

Dietary Health, Magnesium Intake, Metabolic Syndrome, Monoamine Hypothesis, Neurological Disorders, Oxytocin Receptor

1. Introduction

The monoamine hypothesis of depression explains how applying the pharmacological therapy for depression involves increasing the amount of monoamines, dopamine, epinephrine, norepinephrine, and serotonin in an individual's neurochemistry. The monoamine theory of depression has been the prevailing hy-

pothesis in understanding the pathophysiology of depression and has been the primary antecedent behind the development and implementation of psychopharmacological treatments for over five decades [1]. It has also given birth to multiple generations of antidepressant psychotropic medications [2]. In addition, the monoamine hypothesis also functions as a basis of explaining how electrical dysfunction can be the cause of neurological disorders, and is also implicated in regulatory dysfunction related to synaptic and central acting monoamine concentrations of dopamine, epinephrine, norepinephrine, and serotonin [1]. Hinz *et al.* (2012) argue that the bundle damage theory provides a more accurate explanation for chronic dysfunction. This theory proposes that the measure of synaptic monoamines is sufficient but not abundant in conditions associated with continuing electrical dysfunction. Therefore, the amount of synaptic monoamines must be elevated to adjust for the electrical disruptions caused by the destruction to them. While the bundle damage hypothesis challenges the monoamine theory of depression as the foremost explanation for electrical and synaptic disruptions that occur during depressive episodes.

In addition to monoamines, there is a possibility of deficiencies in the neurotransmitter gamma aminobutyric acid (GABA) influencing depression as well [3]. In fact, it has been proposed that the deamination of the neurotransmitter gamma aminobutyric acid GABA, lacking in depression, by brain MAO may have clinical significance for the treatment of depressive disorders [3].

The metabolic syndrome (MetS) is a complex disorder that combines obesity, dyslipidemia, hypertension, and insulin resistance [4]. It is likely that MetS as a whole (insulin resistance, abdominal obesity, atherogenic dyslipidemia, and hypertension) may be a bigger risk indicator than any single MetS factor for adverse health outcomes such as stroke, Alzheimer's disease, and depression [4]. MetS and cardiovascular (CV) risk factors influence CV mortality as well.

A key anxiety and stress regulator is the OXTR, which is a receptor of oxytocin. And may be controlled by both psychosocial factors and gonadal hormones [5].

Kimmel *et al.* (2016) examined serum hormone and postpartum depressive disorder (PPD)-specific DNA methylation variation in the OXTR. The investigators proposed that OXTR DNA methylation is related to PPD at significant locations of their area of function. In particular, those women who were physically or sexually abused as children would have higher rates of PPD [5].

O'Neil *et al.* (2014) discovered a strong association between unhealthy diet (an increase in the intake of saturated fats, refined carbohydrates, and processed food products) and a decline in the psychological health in both children and adolescents. The researchers also found a positive relationship between good-quality diet (vegetables, salads, fruits, fish, and other healthy food groups) and better mental health [6]. Rosique-Esteban *et al.* (2018) discovered a negative relationship between magnesium (Mg) consumption and cardiovascular diseases (CV). The researchers also concluded that elevated consumption of Mg is linked with lower risk of major CV risk factors (mainly metabolic syndrome, diabetes, and hyper-

tension), stroke, and overall cardiovascular disease (CVD) [7]. Similarly, higher rates of circulating Mg are associated with lower risk of CVD, mainly ischemic heart disease and coronary heart disease [7].

2. Objectives

The objective of this paper is to examine several theories that attempt to explain the nature of biochemical changes in the brain as well as metabolism of individuals who experience symptoms and conditions related to neurological disorders like depression. In particular, this paper will review multiple studies that investigate the monoamine (MAO) hypothesis of depression and metabolic syndrome (MetS) as a risk factor for neurological disorders. Any effort to categorize a singular cause for a diverse disorder like depression would be an oversimplification of the general understanding of this complex disorder. Therefore, further investigation through deployment of hypotheses (*i.e.*, GABA deficiency, metabolic syndrome, and oxytocin receptor) may reveal more insights into the causes of depression and help researchers find effective treatments for them.

3. Material and Methods

The systematic literature review for this study was executed in the NCBI and PubMed databases. The papers included published studies up until the year 2021, and are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (PRISMA) (**Figure 1**) [8]. The search included the keywords neurological disorders, monoamine hypothesis, metabolic syndrome, oxytocin receptor, dietary health, and magnesium intake. Excluding those that did not involve symptoms of neurological disorders. Twenty-five research articles were consulted and met the criteria for the literature review of this examination.

4. Results

The Monoamine Hypothesis of Depression

For over half a century the majority of psychopharmacological research devoted to the treatment of depression, has relied on the monoamine hypothesis as the basis of study. It has given birth to several generations of antidepressant medication. Unfortunately, there are severe disadvantages to the present day monoamine theory. Other mechanisms including hypothalamic–pituitary–adrenal (HPA) axis dysfunctions, in addition to neurodegenerative and inflammatory alterations are possibly linked to the pathogenesis of mood disorders [2]. The adjustment to stressors in the environment is one of the key processes of biological regulation. Being exposed to constant stress involves the long-term dysregulations at neurotransmitter, neurohormone, and cellular levels, which can result in changes of behaviors. In turn, metabolism is controlled by sophisticated physiological and behavioral systems, regulated by the brain. Which are influenced by a variety of effectors that include endocrine and immune regulations, neural

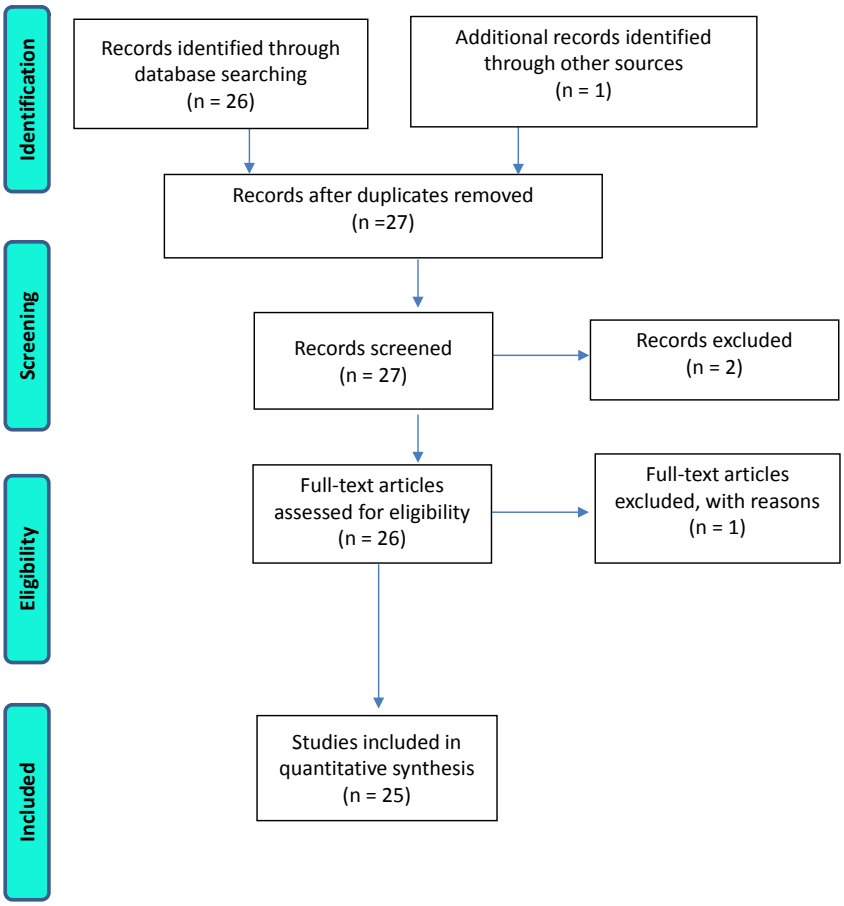

Figure 1. PRISMA flow chart Identifying the search, selection, and inclusion of the articles of the systematic literature review.

plasticity, circadian rhythms, and chromatin modulations. In the past, some studies suggest that these systems are inter-connected and may be the cause of brain disorders in specific mood-related syndromes [2]. While the disturbance of the metabolism of neurotransmitters, circadian clock genes, and modifications of chromatin act together and undoubtedly determine, to some point, behavioral related disorders. The control of chromatin, manifestation of clock genes, and neurotransmitter metabolic processes, are all three assumed to be implicated in mood disorders and HPA axis regulation, and located in an altered state in GR-i mice. Therefore, it is crucial to understand the precise nature of various alterations of these structures as well as their associations, in order to construct novel clinical approaches for treating depression [2].

The monoamine hypothesis has also served as a primary basis for comprehending how electrical dysfunction related with states of pathology and regulatory dysfunction linked to synapses that consists of high levels of centrally-behaving monoamines, dopamine, epinephrine, norepinephrine, and serotonin [1]. It also describes how reduced levels of synaptic monoamines are a main cause of disease, but unfortunately does not provide an acceptable key reference point for understanding chronic electrical dysfunction associated with central-

ly-acting monoamines [1]. The hypothesis adds that the bundle damage theory is a more precise model for comprehending chronic dysfunction. It is the bundle damage theory that suggests that the levels of synaptic monoamines are normal but not sufficient enough in states related to chronic dysfunction. Therefore, the amount of synaptic monoamines must be raised to maintain the balance for the persistent postsynaptic electrical dysfunction, as a result of existing loss [9]. However, the monoamine hypothesis does not explain the etiology of chronic neuronal electrical flow by dysfunction in the endogenous state [1].

5. Gamma Aminobutyric Acid

This discussion reveals how the inhibitory neurotransmitter gamma aminobutyric acid (GABA) and monoamines contribute to depression. The potential of hydrogen level (pH) of cerebral spinal fluid (CSF) closely approximates the isoelectric point of GABA, and there is good evidence to support small quantities of lipophilic GABA micro species in CSF. Initial results determine that deamination of non-physiologic amounts of GABA is catalyzed by MAO [3]. Regardless if the amount of lipophilic GABA and deamination materials may be very small, in the environment of the central nervous systems, where minute reductions in GABA may demonstrate clinical significance [3]. If evidence for these ideas can be discovered, even with the known autonomic risks, treatment with monoamine oxidase inhibitor's (MAOI) may be offered sooner in the application of pharmacotherapy for depression [3].

6. Metabolic Syndrome

In general, metabolic syndrome is a common cause of neurological disorders. Metabolic syndrome (MetS) is a cluster of pathologies: abdominal obesity, dyslipidemia, and hypertension (neurochemical changes). At the molecular level, MetS is accompanied by dysregulation in the expression of adipocytes (cytokines and chemokines) and alterations in levels of leptins, a peptide hormone released by white adipose tissue [10]. These changes modify immune response and inflammation that can lead to changes in the hypothalamic/bodyweight/appetite/satiety set point. This results in the imitation and advancement of MetS. The molecular mechanism underlying the mirror relationship between MetS and neurological disorders are not very well understood. It appears that all cellular and biochemical alterations observed in metabolic syndromes like impairment of endothelial cell function, abnormality in essential fatty acid metabolism, and alterations of lipid mediators along with abnormal insulin/lipid signaling may represent a pathological bridge between MetS and neurological disorders like stroke, Alzheimer's disease, and depression. This paper discusses the involvement of the brain in the pathogenesis of MetS and neurochemical changes in stroke, Alzheimer's disease, and depressions [4].

MetS is a cluster of metabolic and cardiovascular (CV) risk factors that include, obesity and visceral adiposity, insulin resistance, dyslipidemia, and hyperten-

sion that lead to risks of CV mortality [11]. While Medina *et al.* (2018) discussed interactions between MetS and autoimmune rheumatic diseases (ARD) in their study [12]. They identified interactions between metabolic and immune systems, where those interactions are regulated between genetics, nutritional status, and intestinal microbiome, where changes in immune-metabolic communication lead to the occurrence of disorders of the autoimmune system. Adipokines are cytokines (cell signaling proteins) secreted by adipose tissue and exert a variety of metabolic activities that contribute to the etiopathogenesis of MetS and are involved in the regulation of both inflammatory processes and autoimmunity in rheumatic diseases. Patients with autoimmune diseases like gout and those with ARD including but not limited to systematic lupus erythematosus, rheumatoid arthritis, antiphospholipid syndrome, ankylosing spondylitis, and vasculitis have an increased prevalence of MetS.

7. Oxytocin Receptor DNA Methylation in Postpartum Depression

Psychosocial factors may be associated with postpartum depression (PPD) for those women who experienced physical or sexual abuse or trauma as children. This is evident by a significant increase in DNA methylation on the oxytocin receptor gene (OXTR) [5]. These women are more likely to develop PPD which affects anywhere from 10% to 20% of women, who experienced physical or sexual abuse or trauma as children and can lead to significant distress in both mother and child. In fact, PDD affects 30% of women with a history of depression and 52% of women with the bipolar disorder. There is also evidence that an increased sensitivity to change in gonadal hormone levels may modulate biological vulnerability to PPD, especially, in regard to estrogens [5]. Kimmel *et al.* (2016) claim it is not the level of estrogens but the differences in downstream responses and psychological consequences to them that may make it risky for vulnerable women. In fact, some of these relationships may suggest a sophisticated interaction among systems of dysregulated hormones and their downstream consequences, specifically, hormones associated with estrogen signaling including progesterone, its metabolites, and oxytocin.

There has been increased speculation in the involvement of the oxytocin (OXT) system in PPD, because it is a hormone of crucial importance in the instigation of maternal behavior after parturition [13]. Another factor is where diminished OXT levels of prenatal plasma have been observed in cases of PPD [14]. The authors propose the oxytocin receptor (OXTR) as an attractive candidate for study of epigenetic variation associated with PPD as modulation of the OXT system occurs with estrogen at the OXTR [5]. It has also been found that the female hormone estradiol increases OXTR gene transcription [15], which leads to increases within the uterus [16] and various areas of the brain like the hippocampus, amygdala, and arcuate nucleus [17]. While Bell *et al.* (2015) have provided details of DNA methylation links of the OXTR with PPD [18]. The as-

sociation involved an interaction of OXTR genotype at rs53576 and epigenetic factors such that antenatal euthymic women who developed PPD had increased OXTR DNA methylation in GG homozygotes [5].

Along with biological evidence, there is epidemiological evidence that may account for a separate set of risk factors for perinatal depression. Whereas antenatal depression and PPD each demonstrate evidence of psychosocial risk factors such as diminished amount of partner and social support [19]. While a woman's history of trauma can influence the onset of PPD [20]. In an assessment and evaluation of studies from 2000 to 2013, Yim *et al.* (2015) discovered substantial risks for the development of PPD related to factors of, chronic strain and stress, severe life stressors, quality of relationships, and romantic partner and maternal support [21]. The biological and epidemiological data lends support to the hypothesis that stressors associated with childbirth and caring for a newborn in the postpartum period may interact with underlying biological risk factors that result in the onset of depressive symptoms. It is also important to recognize that the OXT system may be modified for different outcomes. For example, protective factors like social support can influence the modification of the OXT system as well as the risk factors such as early trauma or severe life events. In terms of risk factors for depression that may lead to depressive episodes or symptoms, the physiological result of estrogen sensitivity and a lack of social support may lead to physiological changes that may result in a depressive phenotype.

Due to the fact that the OXT system is implicated in the process of social bonding and a coping mechanism for anxiety and stress, the oxytocin receptor itself may be a viable resource for linking the influence between the psychosocial stressors and estrogen sensitivity in PPD and antenatal depression. In some past experiments with rats, the blocking of OXTR in progesterone withdrawal model, led to increased hypothalamic pituitary adrenal (HPA) axis activation [22]. Another study showed that OXT administration inhibited stress activation of the HPA axis through recruitment of GABAergic neurons [23]. While in human beings, it has been demonstrated that a substantial amount of childhood trauma on OXT administration induced mood [5]. In terms of genetic influences, it has been found that genetic variations in the OXTR together with early life adversity and therefore a strong predictor of anxious and depressive symptoms [24].

8. Dietary Health and Child and Adolescent Mental Health

There may exist a relationship between dietary health and mental health in both children and adolescents. Children whose diet consist of unhealthy foods like increased saturated fat, refined carbohydrates, and processed food products usually have poorer mental health irrespective of their socioeconomic status (SES). In contrast, children who consume higher rates of healthy foods like vegetables, salad, fish, fruits, and other foods tend to be healthy and also enjoy better mental health [6]. O'Neal *et al.* concluded that diets that are rich in fat and sugar may influence proteins which are implicated in certain developing processes of the

brain, like the signaling molecule brain-derived neurotrophic factor (BDFN). Brain-derived neurotrophic factor is often reduced in individuals with symptoms of depression, and increasing its production lowers symptoms of depression. To the contrary, considerable evidence exists that high quality diets of food packed with nutrients and increased consumption of saturated fats and refined carbohydrates are each exclusively associated with depressive symptoms, which may suggest the possibility of separate operant pathways [6].

9. Dietary Magnesium and Cardiovascular Disease

Research studies suggest a relationship involving magnesium (Mg) intake and cardiovascular risk factors (CV) and cardiovascular disease (CD) [7]. The review of epidemiological studies [7], indicates a link between high Mg intake and lower risk of major CV risk factors such as metabolic syndrome, diabetes, hypertension, stroke and total CVD. Higher levels of circulating Mg have been found to be related to a decreased risk of rates of CVD, primarily coronary and ischemic heart disease [7].

Mg provides an important mineral for the function of human health and is deeply involved in metabolic processes including adenosine triphosphate (ATP)-dependent biochemical reactions, synthesis of DNA and RNA expression, the signaling of cells at both muscle and nerve levels, and together in blood and glucose pressure control [7].

Rosique-Esteban *et al.* (2018) claim that Mg intake is implicated in the risk of CVD and CV risk factors including type 2 diabetes (T2D), MetS or hypertension, and overall mortality. They add that chronic Mg deficiency is associated with increased risk of cardio-metabolic disorders. This study demonstrates that higher MG intake, through diet or supplements, protects against major CV risk factors, MetS, T2D and hypertension, stroke, and overall CVDs.

10. Discussion

This review identifies significant relationships between biochemical changes in the brain and the metabolism of the human body that may influence neurological disorders, metabolite syndrome, and cardiovascular diseases. Even though the monoamine hypothesis of depression is not settled yet, there seems to be evidence that dopamine, epinephrine, norepinephrine, and serotonin do influence symptoms of depression though do not provide complete explanation for depression. The monoamine hypothesis has served as a major reference point for the understanding of electrical dysfunction related to neurological disorders as well as regulatory dysfunction associated with synaptic and the central acting monoamine concentrations of dopamine, epinephrine, norepinephrine, and serotonin.

However, the bundle damage theory suggests a different explanation for chronic dysfunction. The theory claims synaptic monoamine levels are normal but are not adequate enough in states related to chronic electrical dysfunction. The

synaptic monoamine levels must be increased to compensate for the chronic postsynaptic electrical dysfunction from existing damage. It is clear that the bundle damage theory challenges the status of monoamine hypothesis of depression as a reference point for synaptic and electrical dysfunction [1]. There may be evidence that a reduction in the amount of the neurotransmitter GABA may induce depression [3]. In fact, it has been hypothesized that the deamination of the neurotransmitter GABA, deficient during depression, by brain MAO may have clinical significance for the treatment of depression [3]. The excessive deployment of the monoamine hypothesis as the main reference point for the explanation and treatment of depression is noted for its lack of efficacy, given the low rate of success when reuptake inhibitors are used as the primary pharmacological treatment [1]. Hinz *et al.* (2012) remind us that double-blind placebo-controlled studies have steadily demonstrated the efficacy of rates of reuptake depression at 7% to 13% more than the patients in placebo groups treated with reuptake inhibitors. This may suggest according to the reuptake monoamines current hypothesis that blocking transporter reuptake leads to increased concentrations of synaptic monoamines and restoration of electrical flow is not very effective [1]. Hinz *et al.* (2012) add that monoamines cannot cross the blood brain barrier. However, this is not the case for the amino acids, precursors to the dopamine and serotonin, L-dopa and serotonin. The amino acids freely travel through the blood brain barrier to synthesize into their specific monoamines without biofeedback inhibition.

The metabolic syndrome (MetS) is a complex disorder that combines obesity, dyslipidemia, hypertension, and insulin resistance. It is likely that MetS as a whole (insulin resistance, abdominal obesity, atherogenic dyslipidemia, and hypertension) may be a bigger risk indicator than any single MetS factor for adverse health outcomes such as stroke, Alzheimer's disease, and depression [25]. MetS and cardiovascular (CV) risk factors influence CV mortality as well. It is apparent that this complex set of metabolic disorders is multifaceted, and early assessment and detection may reduce or even eliminate these risk factors.

It is the oxytocin receptor (OXTR) that is a primary regulator of anxiety and stress, and may be influenced by both psychosocial factors and gonadal hormones [5]. This study has examined serum hormone and postpartum depressive disorder (PPD)-specific DNA methylation variation in the OXTR., while the hypothesis is that OXTR DNA methylation is associated with PPD at functionally relevant loci [5]. In particular, women who were physically or sexually abused as children would have higher rates of PPD [5]. It is clear that stress and anxiety can influence an epigenetic change in the production of oxytocin and expression of women who experience physical or sexual abuse or trauma in contrast to women who did not, while these victims were more likely to present with symptoms of postpartum depression [26]. While postpartum depression is more likely in such female victims, it is not guaranteed as other physiological and psychosocial factors associated with individual women matter, too.

As far as diet and mental health are concerned, there is a negative relationship between unhealthy diet (increased saturated fats, refined carbohydrates, and processed food products) and poorer mental health for both children and adolescents. On the other hand, good-quality diet (vegetables, salads, fruits, fish, and other healthy food groups) improve mental health [6].

A separate dietary study discovered inverse associations between magnesium (Mg) intake and cardiovascular diseases (CV). While increased rate in the consumption of Mg is related to a decreased risk of developing a major CV risk factors (*i.e.*, diabetes, hypertension, and metabolic syndrome, stroke, and total CVD) The examination also discovered that increased levels of Mg are related to a lower risk of CVD, chiefly coronary and ischemic heart disease [7].

11. Conclusion

It is unrealistic to believe that any effort to rely on a single theory like the monoamine hypothesis of depression to explain a diverse neurological disorder like depression is an oversimplification of the general nature of this multifaceted and multidimensional disease. Therefore, other hypotheses such as GABA deficiency, metabolic syndrome, and oxytocin receptor deserve investigation as they may reveal more information about the causes of depression and other neurological disorders, in order to assist clinicians and researchers to develop more effective clinical treatments for neurological disorders.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Hinz, M., Stein, A. and Uncini, T. (2012) The Discrediting of the Monoamine Hypothesis. *International Journal of General Medicine*, **5**, 135-142. https://doi.org/10.2147/IJGM.S27824

[2] Massart, R., Mongeau, R. and Lanfumey, L. (2012) Beyond the Monoaminergic Hypothesis: Neuroplasticity and Epigenetic Changes in a Transgenic Mouse Model of Depression. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **367**, 2485-2494. https://doi.org/10.1098/rstb.2012.0212

[3] Goldberg, J.S., Bell, C.E. and Pollard, D.A. (2014) Revisiting the Monoamine Hypothesis of Depression: A New Perspective. *Perspectives in Medicinal Chemistry*, **6**, 1-8. https://doi.org/10.4137/PMC.S11375

[4] Farooqui, A.A., Farooqui, T., Panza, F. and Frisardi, V. (2012) Metabolic Syndrome as a Risk Factor for Neurological Disorders. *Cellular and Molecular Life Sciences*, **69**, 741-762. https://doi.org/10.1007/s00018-011-0840-1

[5] Kimmel, M., Clive, M., Gispen, F., Guintivano, J., Brown, T., Cox, O., Beckmann, M.W., Kornhuber, J., Fasching, P.A., Osborne, L.M., Binder, E., Payne, J.L. and Kaminsky, Z. (2016) Oxytocin Receptor DNA Methylation in Postpartum Depression. *Psychoneuroendocrinology*, **69**, 150-160. https://doi.org/10.1016/j.psyneuen.2016.04.008

[6] O'Neil, A., Quirk, S.E., Housden, S., Brennan, S.L., Williams, L.J., Pasco, J.A. and Jack, F.N. (2014) Relationship between Diet and Mental Health in Children and Adolescents: A Systematic Review. *American Journal of Public Health*, **104**, e31-e42. https://doi.org/10.2105/AJPH.2014.302110

[7] Rosique-Esteban, N., Guasch-Ferré, M., Hernández-Alonso, P. and Salas-Salvadó, J. (2018) Dietary Magnesium and Cardiovascular Disease: A Review with Emphasis in Epidemiological Studies. *Nutrients*, **10**, 168. https://doi.org/10.3390/nu10020168

[8] Brennen, S.E. and Munn, Z. (2021) PRISMA 2020: A Reporting Guideline for the Next Generation of Scientific Reviews. *JBI Evidence Synthesis*, **19**, 906-908. https://doi.org/10.11124/JBIES-21-00112

[9] Lepeta, K., Lourenco, M.V., Schweitzer, B.C., Martino Adami, P.V., Banerjee, P., Catuara-Solarz, S., de La Fuente Revenga, M., Guillem, A.M., Haidar, M., Ijomone, O.M., Nadorp, B., Qi, L., Perera, N.D., Refsgaard, L.K., Reid, K.M., Sabbar, M., Sahoo, A., Schaefer, N., Sheean, R.K., Suska, A., Seidenbecher, C., *et al.* (2016) Synaptopathies: Synaptic Dysfunction in Neurological Disorders—A Review from Students to Students. *Journal of Neurochemistry*, **138**, 785-805. https://doi.org/10.1111/jnc.13713

[10] Shi, J., Fan, J., Su, Q. and Yang, Z. (2019) Cytokines and Abnormal Glucose and Lipid Metabolism. *Frontiers in Endocrinology*, **10**, Article No. 703. https://doi.org/10.3389/fendo.2019.00703

[11] Cornier, M.A., Dabelea, D., Hernandez, T.L., Lindstrom, R.C., Steig, A.J., Stob, N.R., Van Pelt, R.E., Wang, H. and Eckel, R.H. (2008) The Metabolic Syndrome. *Endocrine Reviews*, **29**, 777-822. https://doi.org/10.1210/er.2008-0024

[12] Medina, G., Vera-Lastra, O., Peralta-Amaro, A.L., Jiménez-Arellano, M.P., Saavedra, M.A., Cruz-Domínguez, M.P. and Jara, L.J. (2018) Metabolic Syndrome, Autoimmunity and Rheumatic Diseases. *Pharmacological Research*, **133**, 277-288. https://doi.org/10.1016/j.phrs.2018.01.009

[13] Stuebe, A.M., Grewen, K., Pedersen, C.A., Propper, C. and Meltzer-Brody, S. (2012) Failed Lactation and Perinatal Depression: Common Problems with Shared Neuroendocrine Mechanisms? *Journal of Women's Health*, **21**, 264-272. https://doi.org/10.1089/jwh.2011.3083

[14] Skrundz, M., Bolten, M., Nast, I., Hellhammer, D.H. and Meinlschmidt, G. (2011) Plasma Oxytocin Concentration during Pregnancy Is Associated with Development of Postpartum Depression. *Neuropsychopharmacology*, **36**, 1886-1893. https://doi.org/10.1038/npp.2011.74

[15] Mamrut, S., Harony, H., Sood, R., Shahar-Gold, H., Gainer, H., Shi, Y.-J., Barki-Harrington, L. and Wagner, S. (2013) DNA Methylation of Specific CPG Sites in the Promoter Region Regulates the Transcription of the Mouse Oxytocin Receptor. *PLoS ONE*, **8**, e56869. https://doi.org/10.1371/journal.pone.0056869

[16] Franczak, A., Staszkiewicz, J., Koziorowski, M. and Kotwica, G. (2002) The Influence of Estradiol and Progesterone on the Concentrations of Uterine Oxytocin Receptors and Plasma PGFM in Response to Oxytocin in Ovariectomized Gilts. *Reproduction Nutrition Development*, **42**, 327-338. https://doi.org/10.1051/rnd:2002029

[17] Quiñones-Jenab, V., Jenab, S., Ogawa, S., Adan, R.A.M., Burbach, P.H. and Pfaff, D.W. (1997) Effects of Estrogen on Oxytocin Receptor Messenger Ribonucleic Acid Expression in the Uterus, Pituitary, and Forebrain of the Female Rat. *Neuroendocrinology*, **65**, 9-17. https://doi.org/10.1159/000127160

[18] Bell, A.F., Carter, C.S., Steer, C.D., Golding, J., Davis, J.M., Steffen, A.D., Rubin,

L.H., Lillard, T.S., Gregory, S.P., Harris, J.C. and Connelly, J.J. (2015) Interaction between Oxytocin Receptor DNA Methylation and Genotype Is Associated with Risk of Postpartum Depression in Women without Depression in Pregnancy. *Frontiers in Genetics*, **6**, Article No. 243. https://doi.org/10.3389/fgene.2015.00243

[19] Jeong, H.-G., Lim, J.-S., Lee, M.-S., Kim, S.-H., Jung, I.-K. and Joe, S.-H. (2013) The Association of Psychosocial Factors and Obstetric History with Depression in Pregnant Women: Focus on the Role of Emotional Support. *General Hospital Psychiatry*, **35**, 354-358. https://doi.org/10.1016/j.genhosppsych.2013.02.009

[20] Meltzer-Brody, S., Bledsoe-Mansori, S.E., Johnson, N., Killian, C., Hamer, R.M., Jackson, C., Wessel, J. and Thorp, J. (2013) A Prospective Study of Perinatal Depression and Trauma History in Pregnant Minority Adolescents. *American Journal of Obstetrics and Gynecology*, **208**, 211.e1-7. https://doi.org/10.1016/j.ajog.2012.12.020

[21] Yim, I.S., Tanner Stapleton, L.R., Guardino, C.M., Hahn-Holbrook, J. and Dunkel Schetter, C. (2015) Biological and Psychosocial Predictors of Postpartum Depression: Systematic Review and Call for Integration. *Annual Review of Clinical Psychology*, **11**, 99-137. https://doi.org/10.1146/annurev-clinpsy-101414-020426

[22] Windle, R.J., Gamble, L.E., Kershaw, Y.M., Wood, S.A., Lightman, S.L. and Ingram, C.D. (2006) Gonadal Steroid Modulation of Stress-Induced Hypothalamo-Pituitary-Adrenal Activity and Anxiety Behavior: Role of Central Oxytocin. *Endocrinology*, **147**, 2423-2431. https://doi.org/10.1210/en.2005-1079

[23] Smith, A.S., Tabbaa, M., Lei, K., Eastham, P., Butler, M.J., Linton, L., Altshuler, R., Liu, Y. and Wang, Z. (2016) Local Oxytocin Tempers Anxiety by Activating GABAA Receptors in the Hypothalamic Paraventricular Nucleus. *Psychoneuroendocrinology*, **63**, 50-58. https://doi.org/10.1016/j.psyneuen.2015.09.017

[24] Myers, A.J., Williams, L., Gatt, J.M., McAuley-Clark, E.Z., Dobson-Stone, C., Schofield, P.R. and Nemeroff, C.B. (2014) Variation in the Oxytocin Receptor Gene Is Associated with Increased Risk for Anxiety, Stress and Depression in Individuals with a History of Exposure to Early Life Stress. *Journal of Psychiatric Research*, **59**, 93-100. https://doi.org/10.1016/j.jpsychires.2014.08.021

[25] Farooqui, A.A. (2013) Lifestyle as a Risk Factor for Metabolic Syndrome and Neurological Disorders. In: Farooqui, A.A., Ed., *Metabolic Syndrome*: *An Important Risk Factor for Stroke*, *Alzheimer Disease*, *and Depression*, Springer, Berlin, 1-34. https://doi.org/10.1007/978-1-4614-7318-3_1

[26] Pope, C.J. and Mazmanian, D. (2016) Breastfeeding and Postpartum Depression: An Overview and Methodological Recommendations for Future Research. *Depression Research and Treatment*, **2016**, Article ID: 4765310. https://doi.org/10.1155/2016/4765310