British Journal of Medicine & Medical Research
13(11): 1-11, 2016, Article no.BJMMR.24181
ISSN: 2231-0614, NLM ID: 101570965

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Role of Adiponectin and Serotonin in Development of Obesity and Therapeutic Implications

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Authors' contributions

This work was carried out in collaboration between both authors. Author ASS designed the study. Author MNNBMA wrote the draft of the manuscript and literature searches. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2016/24181
Editor(s):
(1) Kate S. Collison, Department of Cell Biology, King Faisal Specialist Hospital & Research Centre, Saudi Arabia.
Reviewers:
(1) Li Yao, Zhejiang Chinese Medical University, China.
(2) Mra Aye, Melaka Manipal Medical College, Malaysia.
Complete Peer review History: http://sciencedomain.org/review-history/13296

Review Article

Received 8th January 2016
Accepted 25th January 2016
Published 14th February 2016

ABSTRACT

Obesity is a major health concern worldwide as it provokes other health issues. The rise of obesity cases has started public concern as chronic obesity incidences are closely related to significantly shortened life expectancy. Coronary artery disease, hypertension, liver/biliary disease, osteoarthritis, strokes and type 2 diabetes are the common comorbidities which are closely associated with obesity. Adiponectin is the copious adipokine secreted by the adipose tissue in a human body. It is an anti-inflammatory and vasculoprotective cytokine whereas Serotonin, 5-hydroxytryptamine (5-HT) is a bio amine derived product of the amino acid tryptophan. Adiponectin and serotonin are observed to be the parts of the obesity by indirectly acting on the adipose tissues. The association of adiponectin and serotonin is based on the effect of adiponectin and serotonin on each other activity. Studies showed an elevation of serotonin may down-regulated the expression of adiponectin, which is normally seen in the case of obesity. Also, the factors affecting their activity vary from the molecular to the physical level.

Keywords: Adiponectin; serotonin; obesity; public health.

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1. INTRODUCTION

Obesity is known as the most prevalent condition of inflammatory manifestation of abnormal or excessive body fat accumulation that exacerbates health conditions and stokes mortality rates [1,2]. Globally, obesity is known as a global pandemic [3]. There are more than one billion overweight adults with the measurement of BMI shown >25 kg/m2 and about 600 million obese adults of BMI reading >30 kg/m2 [4]. In addition, the analysis on the global trends of obesity has demonstrated that pattern of worldwide overweight occurring in men is 38% while it is recorded 40% for women. Furthermore, the obese class of women is 15% and 11% in men [5]. Moreover, the rates of obesity in children have been listed as an epidemic in most of the developed countries and subsequently growing worldwide [6,7]. Recent data have shown a tremendous leap of about fourfold rise in childhood obesity prevalence [8].

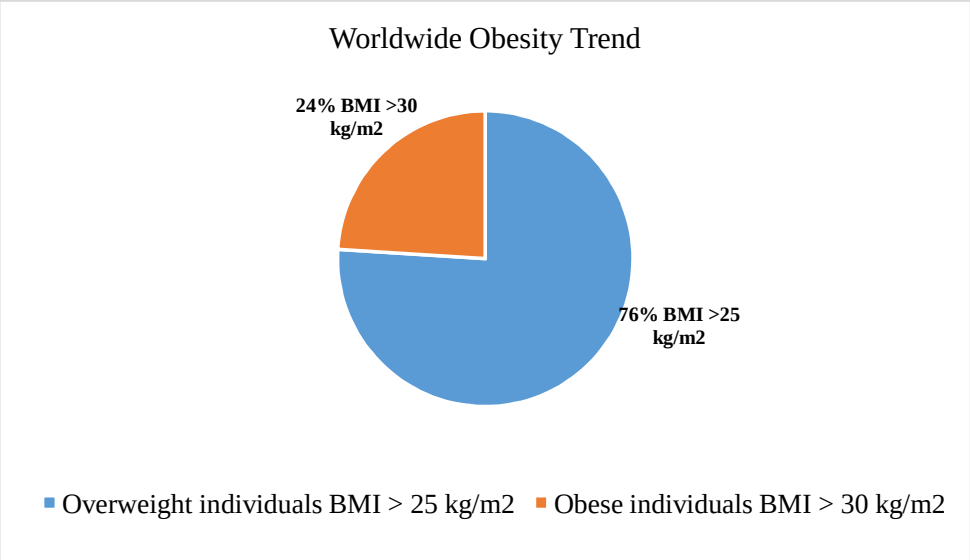

Fig. 1. Shows a pie chart of worldwide overweight and obesity trend [4]

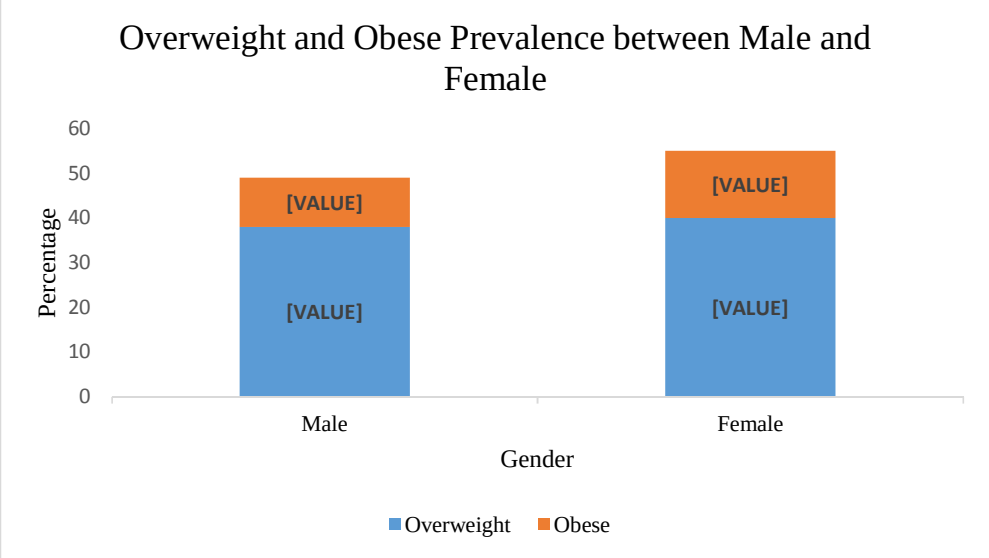

Fig. 2. Shows bar charts of overweight and obese prevalence between male and female [5]

The rise of obesity cases has started public concern as chronic obesity incidences are closely related to significantly shortened life expectancy. Coronary artery disease, hypertension, liver/biliary disease, osteoarthritis, strokes and type 2 diabetes are the common comorbidities which are closely associated with obesity [9–13]. Moreover, it is identified as second leading cause of preventable death behind cigarette smoking [14].

The development of obesity results from the complex relations of genetic, behavioral, environmental associating with economic, social status and lifestyles [15]. Most of the cases observed in the developed countries are attributed to the overabundance fast foods that are energy-laden and convenient with the modern lifestyle. Enhanced intake of saturated fats, carbonated drinks and lack of exercise incorporate to cause obesity [16]. Generally, obesity is induced by long-term energy imbalance due to the sedentary lifestyle and low resting metabolic rate [17].

Besides, heritability is a strong genetic causal component of obesity based on twin studies, family and adoptions with a range around 60% - 90% [18]. Based on genetic studies, parental obesity has shown the highest risk factor [18,19]. However, genetic factors are responsive towards regular physical activity [20] and eating behaviours [21].

Apart from environmental and genetic factors, obesity is closely related to body regulation systems such as growth hormone and reproductive hormone secretion as well as neurological issues. Disturbance of these factors can trigger the development of excess body fat resulting from imbalance of energy intake and energy expenditure [22].

Adipose tissues consist of adipocytes [23,24] that are responsible for heat production (thermogenesis), regulation of body temperature (insulating), cushioning internal organs and energy storage in the form of triglycerides [25]. Moreover, it is a corpulent endocrine organ that secretes numerous pro-/anti-inflammatory or proatherogenic cytokines and adipokines such as adiponectin into the systemic circulation for physiological regulation [26].

Adipocytes secrete multiple hormones called adipokines that are responsible in the metabolism of other organs [27]. In obese subjects, the imbalance of inflammatory adipokines is shown to develop insulin resistance and endothelial dysfunction [28]. Thus, the development of metabolic diseases such as obesity and type-2 diabetes are caused by the impaired clearance of nutrients, elevated lipid output by adipocytes and decreased thermogenesis as well as the distresses of adipokine production [29]. Studies suggested the obese patients have low plasma levels of adiponectin [30].

The aim of writing this review article is to understand the association of adiponectin and serotonin with respect to obesity and the contributing factors on the activity of adiponectin and serotonin. The therapeutic potential of adiponectin and serotonin in the monitoring obesity for future healthcare advances will also be highlighted in this review.

2. ADIPONECTIN

Adiponectin is the copious adipokine secreted by the adipose tissue in a human body. It is an anti-inflammatory and vasculoprotective cytokine [30]. In an animal study using adiponectin-reduced mice, a significant improvement in insulin resistance and hypertriglyceridemia was observed [31]. Adiponectin can increase energy expenditure and fatty acid oxidation that clinically improves insulin sensitivity [30]. Besides, it takes part in glucose homeostasis which makes it an insulin-sensitizing adipokine [31]. Subsequently, the reaction inhibits endogenous glucose production which triggers a transient decrease in basal glucose [32,33].

2.1 Structure

Adiponectin, a 244-amino acid peptide [34], existing in two different structural forms which are full-length adiponectin and globular adiponectin. The globular adiponectin is the result of proteolytic cleavage of the full-length adiponectin [35]. Full-length adiponectin encourages phosphorylation and the activation of 5'-adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscle and the liver, whereas globular adiponectin acts on the skeletal muscle [36]. Globular adiponectin improves fat oxidation and glucose transport as well as activating AMPK activation and acetyl-CoA carboxylase inhibition [37]. Adiponectin has 3 major oligomeric forms which are low-molecular-weight (LMW) rimer, middle-molecular-weight (MMW) hexamer and high-molecular-weight

(HMW) 18-mer [38,39]. Among all, the HMW is the most potent AMPK activator [40].

2.2 Mechanism of Action

As other cytokines, adiponectin conducts its actions through receptors. There are two receptors responsible in mediating the metabolic actions of adiponectin, which are adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) [41]. AdipoR1 is located in the chromosomes 1p36.13-q41 and 1 E4 while AdipoR2 is located at 12p13.31 and 6 F1 [35].

These two receptors are differentiated by their binding affinities for globular and full-length adiponectin even though they have significantly homologous internal N-terminus and external C-terminus in their molecular structures. Both human and mice share 96.8% similarity in AdipoR1 and 95.25% for AdipoR2 [35].

AdipoR1 is associated with AMP-activated kinase (AMPK) activation, whereas AdipoR2 takes place in activating PPARα pathway to enhance insulin sensitivity, fatty-acid combustion and energy consumption [35,41]. Moreover, action of adiponectin via AdipoR1 induces the extracellular Ca2+ influx for Ca2+/calmodulin-dependent protein kinase β (CaMKKβ), AMPK. Consequently, the induction activates Sirtuin 1 (SirT1), enhanced expression and decreased acetylation of PPARϒ coactivator (PGC)-1α and amplified mitochondrial in myocytes [42]. Generally, these receptors serve both globular and full-length adiponectin to mediate increased AMPK, PPARα ligand activities, fatty-acid oxidation, and glucose uptake [41].

2.3 Regulation of Secretion of Adiponectin

Adiponectin often exists in plasma in a small amount in form of globular domain that is cleaved from a full-length form via proteolytic cleavage [43]. The Adiponectin gene that is exclusively expressed in adipocytes is regulated by transcriptional factors such as C/EBPs [44], sterol regulatory element binding protein 1c (SREBP1c) [45] and PPARϒ [46].

Secretion of High Molecular Weight (HMW) Adiponectin has been reported by Farmer et al. begun with the cascade of reaction starting with the depletion of SirT1 levels as well as an elevation of PPARϒ. The chain continues with the increasing of endoplasmic reticulum (ER) oxidoreductase Ero1-L [47].

Another study by Scherer et al has demonstrated that a large amount of precisely folded adiponectin formed a covalent bond with ER chaperone, Erop44 in a secretory pathway through thiol-mediated retention. They also found that another ER chaperone, Ero1-Lα is a vital agent in the secretion of adiponectin from ERp44 as well as playing a role in convening HMW adiponectin [48].

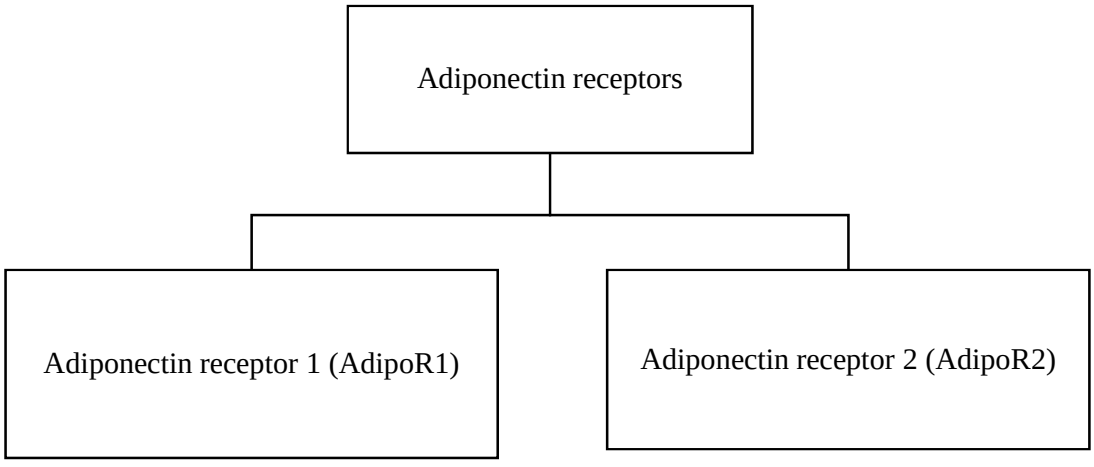

Fig. 3. Shows the types of adiponectin receptors [41]

3. SEROTONIN

Serotonin, 5-hydroxytryptamine (5-HT) is a bio amine derived product of the amino acid tryptophan. Tryptophan is hydroxylated by the enzyme tryptophan hydroxylase (TPH) followed by decarboxylation by aromatic acid decarboxylase (AADC) to form 5 – hydroxytryptamine [49]. In vertebrates, including humans, serotonin is localized in two major pools which are the brain serotonin and the peripheral serotonin. Tryptophan hydroxylase is encoded by Tryptophan hydroxylase 1 (Tph1) and Tryptophan hydroxylase 2 (Tph2) that are expressed in the brain and peripheral cells respectively [50]. Besides, there are distinctive sites of peripheral cells that produce serotonin such as pancreatic beta cells [51,52], adipocytes [53] and osteoclasts [54].

3.1 Structure

As a neurotransmitter, serotonin signaling is mediated by at least fourteen different receptors that are subdivided into seven classes namely 5-hydroxytryptamine receptors 1 to 7 (Htr1 to Htr7). Most of the receptors are G-protein coupled receptors except for Htr3 that is a ligand-gated ion channel receptor. Each G-protein is individually specific to the respective receptor and triggers a distinct intracellular signaling cascade [50].

3.2 Mechanism of Action

Serotonin transporters (SERT) transport extracellular serotonin into the cells to be metabolized. Serotonin activates lipolysis in white adipocytes by binding to its particular Htr2b receptors to stimulate hormone sensitive lipase (HSL). Besides, intracellular metabolites of serotonin also assisted in the signaling process [56]. In brown and beige adipocytes, serotonin stimulation inhibits glucose uptake and studies have proved that locally produced serotonin suppressed adaptive thermogenesis [57,58]. The stimulation of brown adipocytes

Fig. 4. Shows the synthesis of 5-hydroxytryptamine from tryptophan [49]

Table 1. Serotonin receptor subtypes

Serotonin receptors	Serotonin receptors subtypes	Intracellular signaling system	References
5 – HTR 1	5 – HTR 1A 5 – HTR 1B 5 – HTR 1D 5 – HTR 1E 5 – HTR 1F	G-protein coupled receptor	[50,55]
5 – HTR 2	5 – HTR 2A 5 – HTR 2B 5 – HTR 2C	G-protein coupled receptor	
5 – HTR 3	5 – HTR 3A 5 – HTR 3B 5 – HTR 3C 5 – HTR 3D 5 – HTR 3E	Ligand-gated ion channel receptor	
5 – HTR 4	-	G-protein coupled receptor	
5 – HTR 5	5 – HTR 5A 5 – HTR 5B	G-protein coupled receptor	
5 – HTR 6	-	G-protein coupled receptor	
5 – HTR 7	-	G-protein coupled receptor	

inhibits catecholamine beta adrenergic-induced signalling and then the expression of uncoupling protein 1 (Ucp-1) which is the key of thermogenesis promotion in brown adipose tissue (BAT) [58]. Additionally, Htr3a receptor is observed to be involved in the action of serotonin on brown and beige adipocytes [57].

3.3 Regulation of Secretion of Serotonin

Serotonin in human body can be found in the brain and peripheral cells [50]. As the serotonin from these two distinct pools are physically separated by the blood-brain barrier (BBB), they possess distinctly specific functions. Brain serotonin acts as a neurotransmitter to regulate numerous physiological aspects such as behaviour, learning and appetite and glucose homeostasis [51,52,59]. A large amount of the periphery serotonin is produced by enterochromaffin cells of the gut to mediate inflammatory mechanism and gut motility regulation in the intestines [50,60]. In the blood, platelets are the storage site of the serotonin before it is secreted during blood coagulation [50]. Serotonin has also been observed to act on skeletal muscle to influence glucose homeostasis as serotonin receptor Htr2a has been found in the white and red muscle fibres [61]. Generally, peripheral serotonin acts differently based on organs and cell types in the regulation of glucose and lipid homeostasis. Thus, it promotes gluconeogenesis in the liver as well as suppressing hepatic glucose uptake [62]. Likewise, it promotes lipolysis [62], adiponectin production and insulin action in white adipocytes [63]. On the other hand, it acts directly on the brown adipose tissue to suppress thermogenesis and glucose uptake [57,58].

4. ASSOCIATION OF ADIPONECTIN AND SEROTONIN

Earlier study regarding of 5-Hydroxytryptamine 2A (5-HT2A) receptor, which is one of serotonin receptor subtypes, show that the expression of 5-HT2A receptor mRNA was predominant in hypertrophic adipocytes in which consequent decrease of adiponectin expression was noted. In addition, the differentiation of adipocytes is partially modulated by peripheral serotonin acting on HT2A and HT2C receptors [56]. A study reported that the 5-HT2A receptor signaling process produced negative regulation of the adiponectin expression. An observation in adipose tissue of mice showed up-regulation of the expression of 5-HT2A receptors in adipose tissue yet the adiponectin expression was down-regulated. In contrast, the antagonism of the 5-HT2A receptor increases the expression of adiponectin [63,64].

5. FACTORS AFFECTING THE ACTIVITY OF ADIPONECTIN AND SEROTONIN

The activity of adiponectin and serotonin is measured by their levels in the circulation system. There are various factors affecting plasma adiponectin levels, such as insulin, intracellular stress in adipose tissues, hormones, and lifestyle. Whereas, for serotonin, the factors are the alteration of its receptor, and dietary status. Firstly, studies suggested that mutations in the insulin receptor can cause an elevation of plasma adiponectin [65].

Animal studies on the adipocyte-specific insulin receptor knockout mice showed increased adiponectin expression levels in adipose tissue with the absence of functional insulin receptors [66]. In addition, increased serum insulin levels may activate serum reductase that induces the breaking down of high molecular weight (HMW) adiponectin resulting in a short appearance of low molecular weight (LMW) adiponectin. Secondly, intracellular stress in adipose tissue, such as low level of Sirtuin 1 (SirT1), oxidative stress, and inflammation can deplete adiponectin levels [67].

Next, the levels of adiponectin in circulation appear to be different in male and female. Apparently, the female is observed to have higher plasma adiponectin levels than males in both humans and rodent studies. This observation suggested that sex hormones such as testosterone and oestrogen have a part in the regulation of adiponectin [68–70]. Lastly, lifestyle changes such as caloric restriction diet, starvation and fasting have been observed to up-regulate the plasma adiponectin levels [67].

The reduction of serotonin expression in the peripheral system is mainly triggered by the alteration of the serotonin transporter which is commonly the polymorphism of the serotonin transporter [71]. There was a study using the serotonin transporter knockout (5-HTT ko) mice resulted in a reduction of their brain 5-HT levels [72]. In the animal study, a fasted mice showed an upregulation of brain-derived neurotrophic factor (BDNF) which is one of co-regulator of serotonin in energy balance control. Apparently, the up-regulation of BDNF elevates the secretion of serotonin [72].

Table 2. Therapeutic application of adiponectin and serotonin

No	Mechanisms of action	Effects	References
1.	Antagonism of 5-HT2A receptor (Sarpogrelate)	Increases the expression of adiponectin	[39,42,44]
2.	A non-thiazolidinedione (non-TZD) selective peroxisome proliferator-activated receptor ϒ (PPARϒ) agonists (INT 131)	Increases the expression of adiponectin	
3.	A selective 5-hydroxytryptamine receptor subtype 2C (5HT2C) agonist (Lorcaserin)	To regulate feeding behavior	
4.	AdipoR1 and AdipoR2 PPARα activator agonist (Wy-14,643)	Increase the up-regulation of AdipoR1 and AdipoR2	

6. THERAPEUTIC APPLICATION OF ADIPONECTIN AND SEROTONIN TO REDUCE OBESITY

A versatile treatment strategies can be established for obesity-linked diseases such as diabetes with the idea of adiponectin receptor agonist and adiponectin sensitisers [73]. Furthermore, 5-HT2A receptor antagonist may have a potential to increase adiponectin expression in obesity. There was a study where an injection of serotonin was administered in healthy human subjects induces lipolysis followed by an elevation of free fatty acids (FFA) and glycerol in the circulation system [74].

Next, the ablation of adipocytes-specific Htr2b impeded a reduction of FFAs and glycerol levels in the fasted mice blood analysis [75]. There was a selective antagonist of 5-HT2A receptors drug named Sarpogrelate [76] had been reported to significantly increase plasma concentrations of circulating adiponectin in type 2 diabetes and non-diabetic [77]. Serotonin is recognized to be the regulator of the cascade of neuronal functions including appetite control [78]. Thus, it is believed that drug that can regulate the monoamine neurotransmitter such as serotonin are effective in causing weight loss in patients [79]. A drug named Lorcaserin (ADP-356) which is a selective 5-hydroxytrypotamine receptor subtype 2C (5HT2C) agonist is proven to be effective to cut down a weight because the receptor specifically regulates the feeding behaviour.

The lower level of adiponectin level has always been perceived in the case of obesity, thus there are four relevant strategies to reverse the reduction of adiponectin. The first step is to increase the levels of adiponectin in the circulation through the injection of adiponectin and consumption of dietary factors such as soy protein and fish oils [44]. Secondly, compounds that can increase adiponectin expression such as thiazolidinedione (TZD) which is an insulin-sensitizing drug(44). The third method is to activate adiponectin receptors (AdipoRs) with its agonist such as INT 131, which is a non-TZD selective peroxisome proliferator-activated receptor ϒ (PPARϒ) agonists(42). Lastly, to increase the levels of AdipoRs. In obesity, the expression levels of adiponectin receptors are low. Thus, up-regulation of AdipoR1 and AdipoR2 can be induced by its agonist Wy-14,643 through PPARα activation [39].

7. CONCLUSION

Globally, the rate of obesity is currently high and increasing at a steady pace. Thus, studies have been called to identify the factors causing obesity in order to manage the rise of the pandemic. Adiponectin and serotonin are observed to be the parts of the obesity by indirectly acting on the adipose tissues. The association of adiponectin and serotonin is clear based on the effect of adiponectin and serotonin on each other activity. For example, many studies have shown an elevation of serotonin may down-regulated the expression of adiponectin, which is normally seen in the case of obesity. Also, the factors affecting their activity vary from the molecular to the physical. For instance, the hormones and also the eating habits of an individual. Furthermore, we have discussed the therapeutic potential of the adiponectin and serotonin in managing obesity. Variation of drugs either antagonists or agonists for adiponectin and serotonin.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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