IJPSR (2025), Volume 16, Issue 3 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 28 September 2024; received in revised form, 03 November 2024; accepted, 07 November 2024; published 01 March 2025

THE NEUROBIOLOGY OF OVEREATING: DOPAMINE'S ROLE IN OBESITY

Navpreet Kaur [1] and Puja Gulati [*2]

Desh Bhagat University [1], Mandi Gobindgarh - 147301, Punjab, India.
G. H. G. Khalsa College of Pharmacy [2], Guruar Sudhar - 141014, Punjab, India.

Keywords:

Obesity, Gut microbiota, Pathogenesis of obesity, Obesity and neuroinflammation, Brain pathways to obesity, Neurotransmission

Correspondence to Author:
Puja Gulati

Assistant Professor,
G. H. G. Khalsa College of Pharmacy,
Guruar Sudhar - 141014, Punjab, India.

E-mail: pujagulati@deshbhagatuniversity.in

ABSTRACT: Today, obesity has become a global pandemic affecting billions of people worldwide. It is associated with increased risks of various diseases, including cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer, and diabetes, making it a significant public health issue. Obesity has also been linked to an elevated risk of metabolic diseases and changes in brain structure and function. The body mass index (BMI) is widely used to determine excessive weight in relation to height and age. However, BMI may not be accurate for everyone, and BMI z-scores are employed when analyzing data on children and adolescents. The accumulation of excess body fat, which contributes to obesity, is attributed to an imbalance between energy intake and expenditure, controlled by the brain's central nervous system. Disturbances in the brain circuits that regulate energy balance can impact body weight and adiposity, often involving changes in neurotransmission, which may be addressed with CNS-targeting drugs. The pathogenesis of obesity is characterized by a chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure, primarily driven by decreased physical activity. Hormones and peptides produced by the enteric nervous system, such as cholecystokinin, ghrelin, and leptin, influence hunger and fullness, while leptin, an adipocyte-produced hormone, regulates energy expenditure and food intake. In conclusion, Understanding the pathogenesis and physiological mechanisms underlying obesity is crucial for developing effective prevention and intervention strategies.

INTRODUCTION: Today, obesity has been a universal pandemic after affecting billions of people all over the world [1]. Obesity is linked with escalated risks of many diseases such as cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer and diabetes that is a significant public health issue [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.16(3).615-25

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(3).615-25

Excessive number of deaths all over the world are due to obesity and overweight having obesity rates incomparable in many countries [3]. The widespread presence of obesity is now three times from last forty years [4].

Over 1.9 billion individuals aged 18 and older were overweight in 2016, with over 650 million of them being obese. These figures indicate that 39% of people over the age of 18 (39% men and 40% women) were overweight, while 13% of the adult population worldwide (11% men and 15% women) had obesity [5]. Obesity has been linked to an increased risk of metabolic diseases as well as changes in brain structure and function, according

to research [6]. One of the most used methods for determining excessive weight in relation to height and age is the body mass index (BMI). The World Health Organisation divides obesity into four categories based on BMI: underweight (BMI less than 18.5 kg/m2), normal weight (18.5 to 25 kg/m2), overweight (26 to 30 kg/m2), and obese (more than 30 kg/m2) [7]. BMI has traditionally been utilised in adults; however it is now also being used in children and the elderly. Nevertheless, using BMI as an indicator of overweight or obesity is not accurate for everyone. Because BMI changes with age and sex in this group, BMI z-scores are employed when analysing data on children and adolescents [8].

Although, obesity is a complex multifactorial disease, the accumulation of excess body fat is mathematically explained by an imbalance between energy intake and energy expenditure [9]. The brain's central nervous system (CNS) controls these two energy balance equation factors [10]. Abnormalities in the brain circuits that control energy balance have a significant impact on body weight and adiposity [11].

These changes are as complex as fat. However, most, if not all, of these disturbances cause changes in neurotransmission, which can be addressed or improved with CNS-targeting drugs. Obesity's aetiology and pharmacology point to a neurotransmitter problem [12]. The brain's capacity to integrate behavioural, endocrine, and autonomic responses via afferent and efferent channels from and to the brainstem and peripheral organs underlies the control of body weight. The hypothalamus, in particular, is responsible for this ability [13].

Pathogenesis of Obesity: A loss of equilibrium between food intake and energy utilisation leads to obesity [14]. A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity [15]. Energy used up during physical exercise, maintaining essential bodily functions, and diet-induced thermogenesis are all included in energy expenditure. The idea that obesity is brought on by irregularities in metabolic energy expenditure and/or diet-induced thermogenesis has not been substantiated by published studies; instead, data shows that decreased physical activity may significantly contribute to body weight increase [16]. The sympathetic nervous system (SNS) is involved in maintaining homeostasis. Eating, particularly eating excessively carbohydrate, boosts SNS activity whereas fasting decreases it. Lipolysis in adipose tissue is innervated by and modulated by the SNS [17]. By directly affecting the metabolic status of adipose tissue, parasympathetic input has the potential to modulate the aetiology of obesity. The SNS and macrophages must interact in neuroimmune ways for the homeostasis of many tissues, including adipose tissue [18].

The vagus nerve links the brain and digestive system. More than 30 neurotransmitters are produced by the enteric nervous system; these peptides and hormones are released into the circulation, pass across the blood-brain barrier, and stimulate the central nervous system (CNS). Intestinal hormones, including as the peptides cholecystokinin, ghrelin, and leptin, which control the feelings of hunger and fullness, are produced upon ingestion as a result of the stomach's dilation. By blocking vagal signals and repressing the release of insulin, ghrelin increases appetite [19].

The effects on SNS activity are mediated by leptin and insulin. An adipocyte-produced hormone called leptin is increased in obesity. It is an adipokine that controls a variety of physiological processes including immunity, energy expenditure, and food intake [20]. Circulating leptin concentrations serve as a direct indicator of the amount of energy stored in adipose tissue, and they typically promote energy expenditure while lowering appetite [21].

Leptin binds to its receptor in the brain and exerts its effects *via* the neuroendocrine axis. Additionally, it lessens the hyperglycemia brought on by inadequate insulin [22]. Leptin signalling is compromised when obesity progresses, resulting in leptin resistance. Despite having high blood leptin levels in these situations, the hormone is unable to connect to its receptor and regulate physiological activity [23]. Leptin resistance, which inhibits leptin signalling and its subsequent physiological consequences, is also linked to obesity. Despite having high amounts of adipokine in the blood, leptin treatment is unsuccessful in obese individuals because they acquire leptin resistance.

As there are currently no recognised medications for this function, reducing leptin resistance is an attractive research field with promise for weight-loss treatment [24].

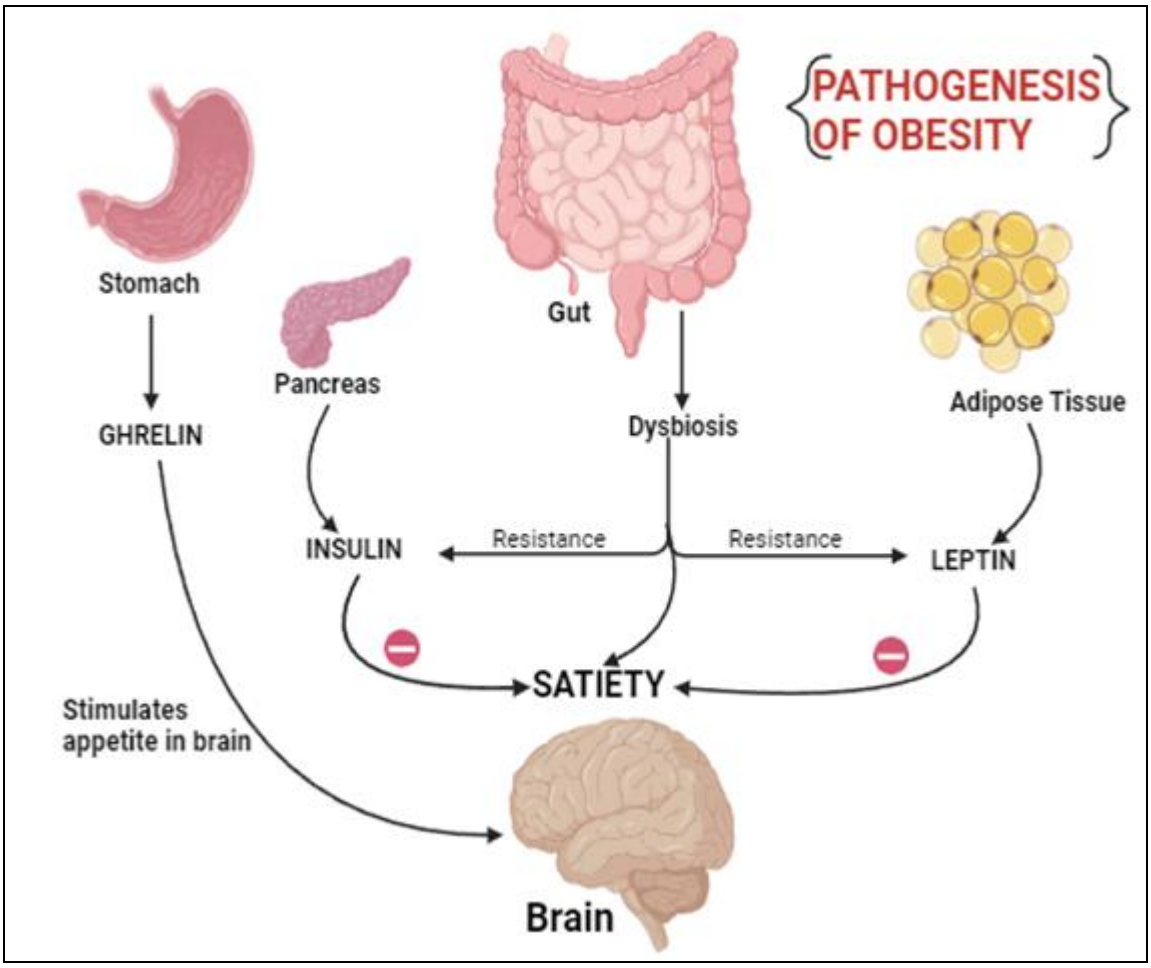

FIG. 1: PATHOGENESIS OF OBESITY

Gut Microbiota: The neurobiological control of eating behaviour is incredibly intricate and involves both motivational and energy homeostasis mechanisms [25-33]. Accordingly, controls that are homeostatic and non-homeostatic have been identified in the neural networks that govern eating behaviour [28, 33]. Homeostatic controls, which traditionally include the hypothalamus and brainstem nuclei, are a response to energy and other metabolic shortages [25, 26]. Hedonic and cognitive components of eating are handled by higher-order brain structures such as frontal cortical areas, mesolimbic circuits, and the hippocampus in non-homeostatic regulation [25, 29]. Additionally, the vagus nerve connects homeostatic and non-homeostatic feeding regulation by transmitting gastrointestinal hunger and satiety signals and modulating higher-order brain regions. The vagus nerve carries information in both directions between the brain and viscera, including the gastrointestinal tract [31-34]. The non-digestible dietary fibres are fermented by the gut microorganisms into short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which are important for metabolism [35]. There was a correlation between obesity and an increase in the Firmicutes/Bacteroidetes ratio [36]. The microbiome's metabolites, which are produced when food is fermented, are crucial in controlling the metabolism of the host. In the colon, the gut bacteria transform bile acid into deoxycholic acid and lithocholic acid, which promote the release of the incretin hormones GLP-1 and insulin, hence increasing energy expenditure [37]. The chemical composition of the microbiome is also related to dietary choline metabolism. Microbiome-mediated trimethylamine-N-oxide (TMAO) synthesis from choline has been linked to metabolic and atherosclerotic diseases [38]. Several intestinal-resident bacteria facilitate the conversion of choline

to the intermediate trimethylamine [39]. The SCFAs generated by gut bacteria influence GLP-1 release, inhibit the inflammatory immune response in the gut, and are implicated in insulin signalling linked to fat formation [40-42]. Additional signs of obesity include indicators for inflammation and intestinal permeability [43]. These two issues are related because increased permeability makes it possible for bacterial byproducts to leak into the bloodstream and cause low-grade inflammation, which is a defining hallmark of obesity and insulin resistance [44].

Brain Pathways to Obesity: A forebrain corticolimbic appetitive network is coupled to autonomic hypothalamus and brainstem neural circuits via the brain regions responsible for the control of energy balance. The so-called anorexigenic pro-opiomelanocortin (POMC) neurons and the orexigenic agouti-related peptide (AgRP) neurons, which co-express neuropeptide Y (NPY), make up the melanocortin system in the arcuate nucleus of the hypothalamus [45]. With the third ventricle and median eminence nearby, these neurons are in a prime location for receiving a number of signals indicative of metabolic status. In fact, these neurons are able to recognise and react to a wide range of circulating hormonal and nutritional signals including fatty acids, insulin, glucagon-like peptide 1, leptin, glucose, and ghrelin [46]. As a result, fasting and other negative energy balance conditions activate AgRP/NPY neurons, whereas positive energy balance states activate POMC neurons [47]. Through their combined actions on the downstream cognate central melanocortin receptors melanocortin receptor 3 and melanocortin receptor 4 (MC4R)], these neurons differently control energy balance. The fact that POMC and MC4R mutations are the most prevalent types of monogenic obesitys confirms the significance of these circuits in controlling body weight [48].

The AgRP/NPY neurons, which are a part of the melanocortin system's opposing arm, control feeding through a variety of methods. These neurons coexpress the rapid inhibitory neurotransmitter GABA as well as AgRP, NPY, and NP [49]. AgRP's effects at MC4R are primarily what cause a rise in body weight and food intake after central injection of the substance [50].

Leptin: White adipose tissue is principally responsible for producing leptin, which is then released into the bloodstream. Higher plasma leptin levels are found in those who have more body fat, and these two variables are positively associated. However, as leptin levels drop by over two thirds following a week of caloric restriction, leptin production is closely linked to energy status [51]. Early research using obese animal models showed that leptin reduces food intake while increasing energy expenditure. Leptin deficiency causes animals to consume more food, expend less calories, and experience severe obesity [52]. However, only a tiny percentage of people are leptin deficient; the majority of people are leptin resistant, raising doubts about the effectiveness of leptin in treating obesity in people [53]. Leptin resistance in humans is evidence indicating people who are more likely to put on weight again after losing it had greater leptin levels, which is associated with poorer leptin sensitivity, than people who successfully maintain their weight [54].

Insulin: The integration of several peripheral metabolic signals depends on insulin. Insulin's ability to suppress NPY and activate POMC neurons makes this possible. Insulin is more readily present in the CNS because to insulin receptors in the blood-brain barrier. The entryway for insulin's entry into the central nervous system is the hypothalamus, particularly the arcuate nucleus, which is abundant in insulin receptors [55]. Mice missing insulin receptors in the CNS are insulin resistant, resulting in increased food intake and the development of diet-induced obesity. Insulin has a role in eating behaviours and consequent body weight maintenance [56].Circulating insulin levels are more strongly connected with visceral fat than subcutaneous fat, in contrast to leptin [57].

Ghrelin: The hunger hormone, ghrelin, decreases POMC neurons while activating NPY and AgRP neurons in the arcuate to increase appetite. Ghrelin counteracts leptin's suppression of NPY and AgRP neurons, while leptin counteracts ghrelin's stimulation of food intake, demonstrating how the two hormones interact [58]. Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems [59]. Axons of POMC, NPY, and AgRP neurons that extend to the dorsomedial nucleus, lateral nucleus,

paraventricular nucleus, and ventromedial nucleus distribute the orexigenic signal to various areas of the hypothalamus and nonhypothalamic regions. Through its interaction with visceral vagal afferent neurons, ghrelin also affects hunger. Leptin and insulin both reduce the activation of NPY neurons caused by ghrelin [60]. Ghrelin levels are lower in obese people than in people of normal weight 194 and are lower in people with greater body fat, insulin, and leptin levels [61].

Obesty and Neuroinflammation: The buildup of glial cells in the brain and spinal cord (CNS) as a reaction to inflammation is known as neuroinflammation. This happens when proinflammatory cytokines (including IL-1 and TNF), cytotoxic substances, and reactive oxygen species (ROS) are secreted by activated astrocytes and microglia as soon as there is damage, which results in neuronal death [59]. Anatomical anomalies occurs in the amount of grey matter in obese people. When obesity is present, there is a continuous decrease in grey matter in the control areas of the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere. Nonetheless, an increase in the amount of grey matter was seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus in the examined studies [62]. A greater body mass index is linked to a reduction in several white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum and cingulum (cingulate gyrus and hippocampus). Local alterations in the white matter fibre tracts linked to elevated body mass index (BMI) provide a connection between the prefrontal and limbic areas, perhaps elucidating the heightened likelihood of cognitive decline and dementia in older adults with obesity [63].

When comparing the diameters of the bilateral caudate with the bilateral thalamus, putamen, and globus pallidus, people who are obese have larger sizes than those who are normal weight [64]. The brain area known as the hippocampus, which controls memory and cognition, is frequently linked to obesity-related cognitive decline. Higher BMI (>30 kg/m2) has been linked in human studies to decreases in white matter integrity and grey matter volume in the hippocampus and other brain regions, underscoring the harmful consequences of obesity on brain structure [65]. Mechanisms *via* which obesity and a bad diet affect cognitive performance.

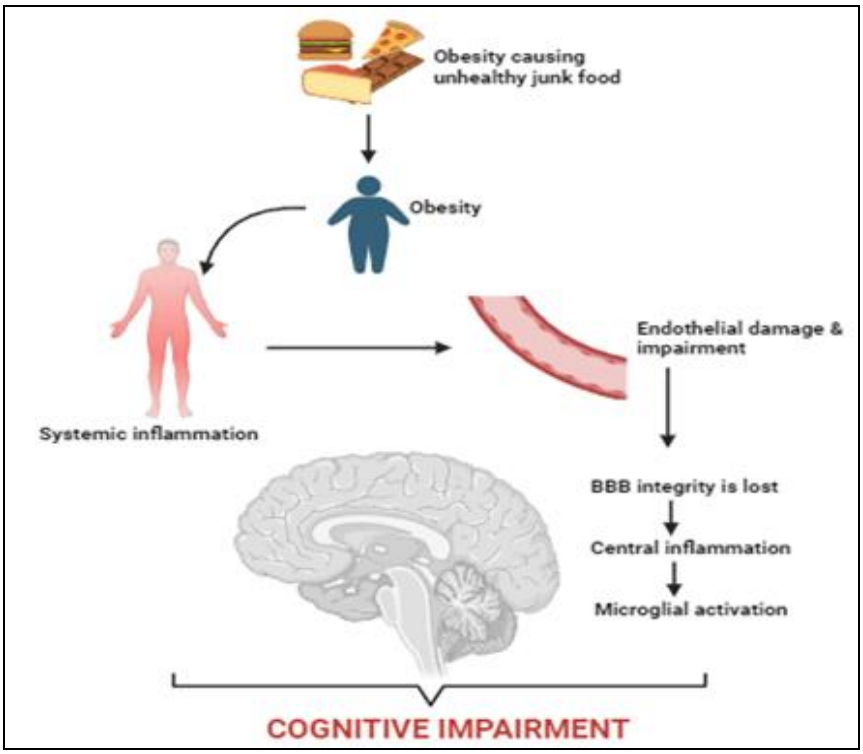

FIG. 2: EFFECT OF BAD FOOD ON COGNITIVE IMPAIRMENT

Obesity and/or poor nutrition leads to low-grade systemic inflammation that compromises the blood-brain barrier, causes central inflammation, activates microglia, and expresses pro-inflammatory proteins. These events cause synaptic remodelling, neuronal death, and decreased neurogenesis. Cognitive impairment is also associated with metabolic dysfunction, insulin resistance, development of white adipose tissue, and changes in the gut flora brought on by obesity. When neurotransmitter systems, including the glutamatergic, cholinergic, and dopaminergic systems, are disrupted, acetylcholine and dopamine levels drop and glutamate signalling becomes dysfunctional. These factors further impair memory, learning, and cognition, ultimately resulting in cognitive impairments [66].

More than 100 identified neurotransmitters are members of a large family of chemical messengers that are involved in synaptic transmission and that control physiological processes in the central and peripheral nervous systems [67]. The most researched neurotransmitters include glutamate, acetylcholine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), dopamine, and serotonin because they have therapeutic significance.

Serotonin: The primary mechanisms controlling feeding action are hedonic and homeostatic systems. The brainstem and hypothalamus are the main areas of the homeostatic system [68]. Other neurotransmitters are also involved in hedonic signalling, but dopamine and serotonin play major roles in it [69-70]. Serotonin, also known as hydroxy tryptamine, or 5-HT, is mostly found in the GI tract, platelets, and the serotoninergic neuronal network of the central nervous system. Serotonin functions as a peripheral hormone in addition to a neurotransmitter. Nonetheless, the intestinal mucosa's enterochromaffin (EC) cells produce the majority of the 5-HT. The human gut is the biggest endocrine organ, producing over 95% of all serotonin [71].

The reward pathway sometimes refers to the mesolimbic system, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA. It has also been suggested that these areas participate in the interplay between hedonic and homeostatic control of food intake [72].

An excess of energy intake over energy expenditure leads to obesity. As a result, it has been hypothesised that eating above one's needs for energy may be facilitated by reduced homeostatic inhibition and/or greater hedonic desire. Those who are chronically overweight or obese may have disrupted eating behaviour as a result of disruptions in serotonergic signalling, as this signalling plays a crucial role in regulating food intake. Indeed, evidence from several research suggests that obesity-related disruptions in serotonergic signalling occur in both humans and animals [73-74].

The human central serotonin system cannot be directly studied *in-vivo*. Serotonin and its metabolites in cerebrospinal fluid (CSF), postmortem immunohistochemistry of brain tissue, and molecular neuroimaging methods like positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have all been used to evaluate alterations in serotonergic signalling linked to obesity in humans [75]. The infundibular nucleus, which is comparable to the ARC in rats, showed lower levels of SERT protein in the post-mortem hypothalamus tissue of overweight/obesity-affected humans [76].

Serotonin (5-HT) has been linked to abnormal signalling in animal models of obesity and is implicated in the control of hunger [77-78]. The findings that, over a 4-week hypocaloric diet, thalamic SERT rose when the majority of daily calories were consumed during breakfast and fell when the majority of daily calories were received during supper suggest that meal time plays a role [79]. According to these research, serotonergic signalling alterations may arise early in the overindulgence in food that occurs in humans, potentially playing a role in the development and/or maintenance of obesity.

In order to manage food intake, the central 5-HT system is essential. Research from the 1970s was actually the first to demonstrate that in rodents, loss of brain 5-HT due to central infusion of 5,7-dihydroxytryptamine, a neurotoxin that specifically kills serotonergic neurons, or p-chlorophenyl alanine, an inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT, causes hyperphagia and obesity.

Medication that affects the central 5-HT system, such as locaserin, is effective in encouraging weight reduction [80-82]. The activation of central serotonergic transmission emerged as a treatment target for obesity well over ten years ago, based on the clear involvement of serotonergic transmission in eating habits and translational studies showing diminished serotonergic transmission in human obesity. Fenfluramine, sibutramine, and subsequently dexfenfluramine were all effectively marketed as therapies for obesity [83].

Dopamine: Molecular imaging studies have shown structural dopamine abnormalities in human obesity, namely in the area of dopamine release and availability of the D2/D3 receptor. However, dopamine synthesis capacity and dopamine reuptake transporters have also been studied [84]. The production and release of DA are regulated by steroid hormones, insulin, leptin, and other peripheral peptides [85]. It seems that DA is connected to the control of food intake on both a short-term (individual meals) and long-term (hunger) time scale [86].

There are five distinct subtypes of DA receptors, which may be divided into D1- (D1, D3) and D2- (D2, D4 and D5) similar subtypes. The regulation of eating behaviour is significantly influenced by both D1- and D2-like receptors. Reduced meal size through shorter eating sessions is the primary outcome of satiety signals, which are facilitated by DA's actions on D1 receptors. The key relationship between DA and D2 receptors is feeding rate. By shortening the length and pace of eating, a combination of DA agonists, such apomorphine, lowers appetite [87].

The gene that codes for the D2 receptors has received the majority of attention in human genetic research on the role of the DA system in obesity. Research conducted on laboratory animals has demonstrated that DA agonists normalised body weight in genetically obese mice (ob/ob) [88]. Human studies have shown a higher prevalence ofthe Taq I A allele for the D2 receptors in obese individuals [89]. Variants of the D2 receptor gene and the human obesity (ob) gene have been investigated in connection to obesity. When combined, these two polymorphisms explain around 20% of the variation in body mass index (BMI, which is calculated by dividing weight in kilogrammes by height in metres), especially in younger women [90]. The Taq I A allele's correlation with less D2 receptors implies that fat people carrying the A1 allele could use food to raise their DA stimulation to a more tolerable level. This is in line with research showing decreased DA metabolite concentrations in cerebral fluid in bulimic individuals who have frequent binge episodes [91].

According to brain imaging studies on obese patients, there was less binding of the tracer [11C] raclopride, which is selective for D2 and D3 receptors, in the striatum of obese subjects compared to controls. This suggests that the availability of D2/D3 receptors is downregulated in obesity. Comparing overweight and obese individuals (BMI > 27 kg/m2) to controls, similar results were found [92-93]. Results on differences in sex and gender in DA release are likewise conflicting. Female controls in a [123I] iodobenzamide SPECT scan responded to amphetamine with considerable DA release, while extreme obese women did not exhibit any meaningful change from baseline [94].

CONCLUSION: Obesity is a global health issue that affects billions of people worldwide, with obesity rates three times higher than in the last forty years. Obesity accumulation is mathematically explained by an imbalance between energy intake and energy expenditure, which is controlled by the brain's central nervous system (CNS). The pathogenesis of obesity involves a loss of equilibrium between food intake and energy utilization. A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity. The sympathetic nervous system (SNS) is involved in maintaining homeostasis, and parasympathetic input has the potential to modulate the aetiology of obesity. The vagus nerve links the brain and digestive system, producing over 30 neurotransmitters that stimulate the CNS.

The gut microbiome ferments non-digestible dietary fibers into short-chain fatty acids (SCFAs), which are important for metabolism. The chemical composition of the microbiome is also related to dietary choline metabolism, and the SCFAs generated by gut bacteria influence GLP-1 release,

inhibit the inflammatory immune response in the gut, and are implicated in insulin signaling linked to fat formation. Inflammation and intestinal permeability are indicators of obesity, as increased permeability allows bacterial by products to leak into the bloodstream and cause low-grade inflammation, a hallmark of obesity and insulin resistance.

Obesity is a complex condition influenced by various factors in the brain. The melanocortin system, composed of anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP) neurons, plays a crucial role in controlling energy balance. These neurons are located near the third ventricle and median eminence, and can recognize and react to various hormonal and nutritional signals. Fasting and other negative energy balance conditions activate AgRP/NPY neurons, while positive energy balance states activate POMC neurons. AgRP/NPY neurons control feeding through GABA, NPY, and NP. Leptin, a hormone produced by white adipose tissue, is closely linked to energy status and can reduce food intake while increasing energy expenditure. Insulin, a hormone that regulates peripheral metabolic signals, is more readily present in the central nervous system due to its blood-brain barrier receptors. Ghrelin, a hunger hormone, decreases POMC neurons and activates NPY and AgRP neurons in the arcuate to increase appetite. Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems.

Obesity and neuroinflammation are linked to the buildup of glial cells in the brain and spinal cord, which results in neuronal death. Obesity leads to a decrease in grey matter in control areas such as the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere, while an increase in grey matter is seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus. Obesity also leads to alterations in white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum, and cingulum. More than 100 identified neurotransmitters are involved in synaptic transmission and control physiological processes in the central and peripheral nervous systems. The reward pathway, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA, participates in the interplay between hedonic and homeostatic control of food intake. Obesity-related disruptions in serotonergic signalling occur in both humans and animals.

Molecular imaging studies have shown structural dopamine abnormalities in human obesity, specifically in the area of dopamine release and availability of the D2/D3 receptor. Dopamine is connected to the control of food intake on both short-term and long-term time scales. There are five distinct subtypes of DA receptors, with the regulation of eating behaviour significantly influenced by both D1- and D2-like receptors. The key relationship between DA and D2 receptors is feeding rate, with a combination of DA agonists like apomorphine lowers appetite. The Taq I A allele, which codes for the D2 receptors, has been linked to obesity, with variations explaining around 20% of the variation in body mass index. Brain imaging studies on obese patients show less binding of the tracer [11C] raclopride, suggesting down-regulation of D2/D3 receptors in obesity.

ACKNOWLEDGEMENT: The authors would like to acknowledge the Desh Bhagat University, Mandi Gobindgarh and G. H. G. Khalsa College of Pharmacy, Gurusar Sadhar for providing all the infrastructure, laboratory facilities and animal experimental facilities respectively.

CONFLICTS OF INTEREST: The authors do not have any conflicts of interests.

REFERENCES:

1. SK KY and Bhat PK: Obesity: another ongoing pandemic. Lancet Gastroenterol Hepatol 2021; 6: 411.
2. Cole D. Bendor and Aya Bardugo: Cardio vascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. Cardiovascular 2020; 19: 79.
3. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults 2024; 403, 10431: 1027-1050.
4. World Health Organization (WHO), Obesity and Overweight, World Health Organization (WHO), Geneva, Switzerland 2020.
5. World Health Organization (WHO), Obesity and Overweight, World Health Organization (WHO), Geneva, Switzerland 2020.

6. Jin Panel Xin and Qiu Tingting: Pathophysiology of obesity and its associated diseases. Acta Pharmaceutica Sinica B 2023; 13(6): 2403-2424.
7. World Health Organization (WHO), Obesity and Overweight, World Health Organization (WHO), Geneva, Switzerland 2020.
8. Ghosh Asia Zierle and Jan Arif: Physiology, Body Mass Index. National Library of Medicine 2023.
9. Hall Kevin D, Farooqi I Sadaf, Friedman Jeffery M, Klein Samuel, Loos Ruth JF, Mangelsdorf David J, O'Rahilly Stephen, Ravussin Eric, Redman Leanne M, Ryan Donna H, Speakman John and Tobias Deirdre K: The energy balance model of obesity: beyond calories in, calories out. The American Journal of Clinical Nutrition 2022; 115(5): 1243-1254.
10. Tran Le Trung, Park Sohee, Kim Seul Ki, Lee Jin Sun, Kim Ki Woo & won Obin K: Hypothalamic control of energy expenditure and thermogenesis. Experimental & Molecular Medicine 2022; 54: 358-369.
11. Manceau R, Majeur D and Alquier T: Neuronal control of peripheral nutrient partitioning. Diabetologia 2020; 63(4): 673-682.
12. García-Cazorla and Artuch R: A Neurotransmitter disorders. Elsevier 2020; 917-929.
13. Elmquist Joel K Elmquist and Coppari Roberto: Identifying hypothalamic pathways controlling food intake, body weight, and glucose homeostasis. Journal of Comparative Neurology 2005; 493: 63-71.
14. Loffler Mona C and Betz Matthias J: Challenges in tackling energy expenditure as obesity therapy: From preclinical models to clinical application. Molecular Metabolism 2021; 51: 101237.
15. Rufina ANB, Oshomegie Hannah and Udenta Elizabeth A: Energy intake, expenditure and balance, and factors associated with energy balance of young adults (20–39 years): a retrospective cross-sectional community-based cohort study. BMC Nutrition 2022; 8: 142.
16. Bourdier Pierre, Simon Chantal, Bessesen Daniel H, Blanc Stéphane and Bergouignan Audrey: The role of physical activity in the regulation of body weight: The overlooked contribution of light physical activity and sedentary behaviours 2022; 24(2): 13528.
17. Wen Xue, Zhang Bohan, Wu Beiyi, Xiao Haitao, Li Zehua, Li Ruoyu, Xu Xuewen & Li Tao: Signaling pathways in obesity: mechanisms and therapeutic interventions. Nature 2022; 7: 298.
18. Martinez-Sanchez Noel, Sweedey Owen, Sidarta-oliveira Davi, Caron Alexandre, Stanley Sarah A and Domingos Ana I: The sympathetic nervous system in the 21st century: Neuroimmune interactions in metabolic homeostasis and obesity.Neuron 2022; 110(21): 3597-3626.
19. Martelli Davide and Brooks Virginia L: Leptin increases: physiological roles in the control of sympathetic nerve activity, energy balance, and the hypothalamic–pituitary–thyroid axis. Inernational Journal of Moecular Sciences 2023; 24(3): 2684.
20. Pico Catalina, Palou Mariona, Pomar Catalina Amadora, Rodríguez Ana María and Palou Andreu: Leptin as a key regulator of adipose organ. Frontiers in Endocrinology 2021; 23: 13-30.
21. Sudar Emina and Soskic Sanja: Leptin and Obesity: Role and Clinical Implication. Secondary Obesity. Frontier of Endocrinology 2021; 12.
22. Liu Tao Xiao Zhaoxun and Liu Hailan: Leptin signaling and its central role in energy homeostasis. Frontier Neurosciences 2023; 17: 23.
23. Gomez Wllliam A and Humeres Gustavo: Leptin signaling and its relationship with obesity-induced insulin resistance: Abioinformatics-assisted Review. Gene Expression 2024.
24. Kim Jae Won, Kim Jun Hyeok and Lee Yoon Jae: The role of adipokines in tumor progression and its association with obesity. Biomedicines 2024; 12(1): 97.
25. Watts Alan G, Kanoski Scott E, Watts Graciela Sanchez and Langhans Wolfgang: The physiological control of eating: signals, neurons, and networks. Physiol Rev 2021; 102(20: 689-813.
26. Hyunju Ahn Benjamin, Kim Minyoo and Kim Sung-Yon: Brain circuits for promoting homeostatic and non-homeostatic appetites. Nature 2022.
27. Watts Alan G, Kanoski Scott E,Watts Graciela Sanchez, and Langhans Wolfgang: The physiological control of eating: signals, neurons, and networks. Experimental & Molecular Medicine 2022; 54: 349-357.
28. Stover Patrick J, Field Martha S, Andermann Mark L, Bailey Regan L, Batterham Rachel L, Cauffman Elizabeth, Frühbeck Gema and Iversen Per O: Reed Pamela Starke: Neurobiology of eating behavior, nutrition, and health. Journal of Medicine 2023; 294(5).
29. Prescott Sara L and Liberles Stephen D: Internal senses of the vagus nerve. Neuron 2022; 110(4): 579-599.
30. Wachsmuth Hallie R, Weninger Savanna N and Duca Frank A: Role of the gut–brain axis in energy and glucose metabolism. Experimental & Molecular Medicine 2022; 54: 377–392.
31. Prescott Sara L and Liberles Stephen D: Internal senses of the vagus nerve. Neuron 2022; 110(4): 579-599.
32. Aljeradat Baha' and Kumar Danisha: Neuromodulation and the Gut–Brain Axis: Therapeutic Mechanisms and Implications for Gastrointestinal and Neurological Disorders. Pathophysiology 2024; 31(2): 244-268.
33. Singh Alpana, Dawson Ted M and Kulkarni Subhash: Neurodegenerative disorders and gut-brain interactions. The Journal of Clinical Investigation 2021; 131(13): 143775.
34. Amanda J: Gastrointestinal Vagal Afferents and Food Intake: Relevance of Circadian Rhythms. Nutrients 2021; 13(3): 844.
35. Mazhar Muhammad, Zhu Yong and Qin Likang: The interplay of dietary fibers and intestinal microbiota affects type 2 diabetes by generating short-chain fatty acids. Foods 2023; 12(5): 1023.
36. Houtman Timothy A and Eckermann Henrik A: Gut microbiota and BMI throughout childhood: the role of firmicutes, bacteroidetes, and short-chain fatty acid producers. Scientific Reports 2022; 12: 3140.
37. Fujisak, Watanabe Yoshiyuki and Tobe Kazuyuki: The gut microbiome:a core regulator of metabolism. Journal of Endocrinology 2023; 256(3).
38. Zhou Yuhua, Zhang Yuwei, Jin Shengkai, Lv Jing, Li Menglu and Feng Ninghan: The gut microbiota derived metabolite trimethylamine N-oxide: Its important role in cancer and other diseases. Biomedicine & Pharmacotherapy 2024; 177: 117031.
39. Tacconi Edoardo, Palma Giuseppe, Biase Davide De, Luciano Antonio Barbieri Massimiliano Nigris Filomena de and Bruzzese Francesca: Microbiota effect on trimethylamine n-oxide production: from cancer to fitness—a practical preventing recommendation and therapies. Nutrients 2023; 15(3): 563.
40. Ashkan Rasouli Saravani, Jahankhani Kasra, Moradi Shadi, Melika Gorgani, Zahra Shafaghat, Zahra Mirsanei, Amirreza Mehmandar and Rasoul Mirzaei: Role of microbiota short-chain fatty acids in the pathogenesis of

autoimmune diseases. Biomedicine & Pharmacotherapy 2023; 162: 114620.
41. Kim Chang H: Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. Cellular & Molecular Immunology 2023; 20: 341–350.
42. Abdalqadir Nyan and Adeli Khosrow: GLP-1 and GLP-2 orchestrate intestine integrity, gut microbiota, and immune system crosstalk. Microorganisms 2022; 10(10): 2061.
43. Keirns Bryant H and Keirns Natalie G: Adverse childhood experiences and obesity linked to indicators of gut permeability and inflammation in adult women. Physiology & Behavior 2023; 271: 114319.
44. Roham Theresa V and Meier T. Daniel: Inflammation in obesity, Diabetes and related Disorders. Immunity 2022; 55(1): 31-55.
45. Caron Alexandre and Michael Natalie Jane: New Horizons: Is Obesity a Disorder of Neurotransmission?. The J of Clinical Endocrinology & Metabol 2021; 106; 12.
46. Clayton Richard W, Badge Robin Lovell and Galichet Christophe: The properties and functions of glial cell types of the hypothalamic median eminence. Frontier Endocrinology 2022; 13: 953995.
47. Yue Qi, Lee Nicola J, IP ChiKin: Agrp-negative arcuate NPY neurons drive feeding under positive energy balance via altering leptin responsiveness in POMC neurons: Cell Metabolism 2023; 35(6): 979-995.
48. JIi Ren Lei and Tao Ya Xiong: Regulation of Melanocortin-3 and -4 Receptors by Isoforms of Melanocortin-2 Receptor Accessory Protein 1 and 2. Biomplecules 2022; 12(2): 244.
49. Zhang Yan, Shen Jiayi, Xie Famin and Liu Zhiwei: Feedforward inhibition of stress by brainstem neuropeptide Y neurons. Nature Communications 2024; 15: 7603.
50. Mahdieh Khodarahmi and Houman Kahroba: Dietary quality indices modifies the effects of melanocortin-4 receptor (MC4R) rs17782313 polymorphism on cardio-metabolic risk factors and hypothalamic hormones in obese adults BMC Cardiovascular Disorders 2020; 20: 57.
51. Suarez Vicente Javier Clemente and Florez Laura Redondo: The role of adipokines in health and disease. Biomedicines 2023; 11(5): 1290.
52. Perakakis Nikolaos, Farr Olivia M and Mantzoros Christos S: Leptin in Leanness and Obesity: Journal of the American College of Cardiology 2021; 77(6): 745-760.
53. Zhao Shangang and Li Na: Leptin reduction as a required component for weight loss. Diabetes 2024; 73(2): 197-210.
54. Andrea A. FlorioKenny Mendoza-Herrera and Moore Maggie: The Leptin System and Diet: A Mini Review of the Current Evidence. Frontier Endocrinology 2021; 12.
55. Yang D and Hou X: Effect of POMC system on glucose homeostasis and potential therapeutic targets for obesity and diabetes. Dove Press 2022; 2939-2950.
56. Zhao Xuefei and An Xuedong Yang Cunqing: The crucial role and mechanism of insulin resistance in metabolic disease. Frontier Endocrinology 2023; 14.
57. Tylutka Anna and Morawin Barbara: Assesment of metabolic syndrome predictors in relation to inflammation and visceral fat tissue in older adults. Scientific Reports 2023; 13: 89.
58. Young Emily R; Jialal Ishwarlal: Biochemistry, Ghrelin Stat Pearls 2023.
59. Desai Dimpi and Dharia Ashni: Ghrelin Paradox: Unlocking New Avenues in Obesity Management. Medscape Diabetes & Endocrinology 2024.
60. Zhang Weifeng, Xiao Dan, Mao Qinwen and Xia Haibin: Role of neuroinflammation in neurodegeneration development. Signal Transduction and Targeted Therapy 2023; 8: 267.
61. Wu Hui and Dai Guochao: Gray matter reduction in bilateral insular mediating adverse psychiatric effects of body mass index in schizophrenia. BMC Psychiatry 2022; 22: 639.
62. Li Lei and Yu: Gray matter volume alterations in subjects with overweight and obesity: Evidence from voxel-based meta-analysis. Frontier Psychiatry 2022; 13.
63. Ma Jiyoung and McGlade Erin C: Overweight/Obesity-related microstructural alterations of the fimbria-fornix in the ABCD study: The role of aerobic physical activity. Journal PloS one 2023; 18(7).
64. Li Guanya Li and Hu Yang Hu: Brain functional and structural magnetic resonance imaging of obesity and weight loss interventions. Molecular Psychiatry 2023; 28: 1466–1479.
65. Chen Ruilin and Cai Guiyan: Body mass index related to executive function and hippocampal subregion volume in subjective cognitive decline. Frontier Aging Neurosciences 2022; 14.
66. Sayyar Amnah Al and Hammad Maha M: Neurotransmitters in type 2 Diabetes and the control of systemic and central energy balance. Metabolites 2023; 13(3): 384.
67. Sayyar Amnah Al and Hammad Maha M: Neurotransmitters in type 2 diabetes and the control of systemic and central energy balance. Metabolites 2023; 13(3): 384.
68. Campos Alejandro and Alejandro John D: Integrative Hedonic and Homeostatic Food Intake Regulation by the Central Nervous System: Insights from Neuroimaging. Brain Sciences 2022; 12(4): 431.
69. Galen Katy A van, Horst Kasper W ter and Serlie Mireille J: Serotonin, food intake, and obesity. Obesity Review 2021; 22(7): 13210.
70. Lewis Robert G, Florio Ermanno ,Punzo Daniela Punzo and Borrelli Emiliana: The Brain's Reward System in Health and Disease. Advances in Experimental Medicine and Biology 2021; 1344: 57-69.
71. Guzel Tomasz and Guzel Dagmara Mirowska: The role of serotonin neurotransmission in gastrointestinal tract and pharmacotherapy. Molecules 2022; 27(5): 1680.
72. William Diana L: The diverse effects of brain glucagon-like peptide 1 receptors on ingestive behavior. British Journal Pharmacology 2022; 179(4): 571-58.
73. Purnell Jonathan Q and Roux Carel W le: Hypothalamic control of body fat mass by food intake: The key to understanding why obesity should be treated as a disease. Diabetes, obesity and metabolism: A Journal of Pharmacology and Therapeutics 2024.
74. Bakshi Arjun and Tadi Prasanna: Serotonin. Biochemistry 2022.
75. Kumar Vijaya and Brianna Mavanji: Orexin, serotonin, and energy balance 2022; 14(1).
76. Conde Kristine, Fang Shuzheng and Xu Yong: Unraveling the serotonin saga: from discovery to weight regulation and beyond. Cell & Bioscience 2023; 13: 143.
77. Wen Xue and Zhang Bohan: Signaling pathways in obesity: mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy 2022; 29897.
78. Han Xueyun: Timing matters: impact of meal timing on daily calorie intake of office workers. Engineering Proceedings 2023; 55(1).
79. Fenfluramine: a plethora of mechanism? Mini Review article. Frontier Pharmacology 2023; 14.

80. Ma Junxing and Wang Ran: n5-HT attenuates chronic stress-induced cognitive impairment in mice through intestinal flora disruption. Journal of Neuroinflammation 2023; 20: 85(79).
81. He Yanlin He and Cai Xing Cai: 5-HT recruits distinct neurocircuits to inhibit hunger-driven and non-hunger-driven feeding. Mol Psychiatry 2021; 26(12): 7211–24.
82. Borroto-Escuela Dasiel O and Ambrogini Patrizia: The role of central serotonin neurons and 5-ht heteroreceptor complexes in the pathophysiology of depression: a historical perspective and future prospects. International Journal of Molecular Sciences 2021; 22(4): 1927.
83. Janssen Lieneke Katharina and Horstmann Annette: Molecular imaging of central dopamine in obesity: a qualitative review across substrates and radiotracers. Brain Sciences 2022; 12(4): 486.
84. Janssen Lieneke Katharina and Horstmann Annette: Molecular imaging of central dopamine in obesity: a qualitative review across substrates and radiotracers. Brain Sciences 2022; 12(4): 486.
85. Casado María E and Collado-Pérez Robert: Recent advances in the knowledge of the mechanisms of leptin physiology and actions in neurological and metabolic pathologies. International Jounral of Molecular Sciences 2023; 24(2): 1422.
86. Hopkins Mark and Beaulieu Kristine: The control of food intake in humans. Endocrine Textbook 2022.
87. Bhatia Anmol, Lenchner Jennifer R and Saadabadi Abdolreza: Dopamine Receptors, Biochemistry. Stat Pearls 2023.
88. Baik Ja-Hyun: Dopaminergic Control of the Feeding Circuit. Endocrinology and Metabolism 2021; 36(2): 229-39.
89. Montalban Enrica and Walle Roman: The addiction-susceptibility taqia/ankk1 controls reward and metabolism through D2 receptor-expressing neurons. Archival Report 2023; 94: 424-436.
90. Akter Raushanara and Afrose Afrina Afrose: A comprehensive look into the association of vitamin D levels and vitamin D receptor gene polymorphism with obesity in children. Biomedicine & Pharmacotherapy 2022; 153: 113285.
91. Viral Nicole Hidalgo and Oyarcel Karina: No association of the dopamine D2 receptor genetic bilocus score (rs1800497/rs1799732) on food addiction and food reinforcement in Chilean adults. Frontiers in Behavioral Neuroscience 2023.
92. Ribeiro Gabriela and Maia Ana: Striatal dopamine D2-like receptors availability in obesity and its modulation by bariatric surgery: a systematic review and meta-analysis. Scientific Report 2023; 13: 4959.
93. Janssen Lieneke Katharina and Horstmann Annette: Molecular imaging of central dopamine in obesity: a qualitative review across substrates and radiotracers. Brain Sci 2022; 12(4): 486.
94. Gilardini Luisa and Croci Marina: Sex differences in cardiometabolic risk factors and in response to lifestyle intervention in prepubertal and pubertal subject with obesity 2024; 12.

How to cite this article:
Kaur N and Gulati P: The neurobiology of overeating: dopamine's role in obesity. Int J Pharm Sci & Res 2025; 16(3): 615-25. doi: 10.13040/IJPSR.0975-8232.16(3).615-25.