Ghrelin mediated regulation of neurosynaptic transmitters in depressive disorders

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ABSTRACT
Ghrelin is a peptide released by the endocrine cells of the stomach and the neurons in the arcuate nucleus of the hypothalamus. It modulates both peripheral and central functions. Although ghrelin has emerged as a potent stimulator of growth hormone release and as an orexigenic neuropeptide, the wealth of literature suggests its involvement in the pathophysiology of affective disorders including depression. Ghrelin exhibits a dual role through the advancement and reduction of depressive behavior with nervousness in the experimental animals. It modulates depression-related signals by forming neuronal networks with various neuropeptides and classical neurotransmitter systems. The present review emphasizes the integration and signaling of ghrelin with other neuromodulatory systems concerning depressive disorders. The role of ghrelin in the regulation of neurosynaptic transmission and depressive illnesses implies that the ghrelin system modulation can yield promising anti-depressive therapies.

1. Introduction
Ghrelin is an orexigenic hormone, isolated from the rat stomach (Kojima et al., 1999). It is synthesized in the body and binds with the growth hormone secretagogue receptor (GHSR). It regulates the somatotropic secretion of hormones from the pituitary gland (Andrews, 2019). GHSR is mainly found in the arcuate nucleus of the hypothalamus (ARC). Ghrelin stimulates orexigenic neuropeptide Y (NPY) in the ARC via GHSR (Delhanty and van der Lely, 2011). In fact, ghrelin enhances food intake, and thus promotes weight gain by the activation of NPY neurons in the ARC, leading to its popular tag “The Hunger Hormone” (Andrews, 2019).

1.1. Ghrelin in Depression
Ghrelin is released by the stomach and many other organs including bowels, kidneys, lungs, thyroid, hypothalamus, and pituitary gland (Kojima et al., 2005). However, it is also found in trace amounts in the various brain regions (Cabral et al., 2017). Ghrelin is prepared and synthesized endogenously from preproghrelin, which also yields obstratin in minute quantities (Zhang et al., 2008). Obstratin produces physiological variations in the body, like the decline in pancreatic secretions and enhancement of memory and cognition (Gargantini et al., 2013). The discovery of ghrelin and its receptors is a milestone achievement that emphasizes ghrelin-related endocrine mechanisms. Ghrelin governs physiological functions such as the predominant hypothalamus nucleus, which regulates hunger, and the ARC (Marino et al., 2011). Ghrelin and its components are synthesized by many adjacent neurons in the third ventricle. These neurons of the ventricles form ghrelin to act within the brain circuitry in different regions (Cowley et al., 2003). Several studies have established the involvement of ghrelin in the regulation and metabolism of glucose (Qian et al., 2019). Few studies demonstrated that ablation of ghrelin does not affect the change in body weight as well as obesity and adiposity, though normalized glucose metabolism and homeostasis (Castañeda et al., 2010).

The significance of ghrelin in the regulation and metabolism implies that it may be useful for regulating normal blood glucose levels, and might be a therapeutic target for diabetes (Shankar et al., 2020). The role of ghrelin was studied in insulin resistance and regulation of glucose which revealed that ghrelin was effective in regulating glucose levels (Chabot
et al., 2014). Similarly, earlier research also stated that exogenous ghrelin administration increases plasma insulin levels in diabetic rats (Elabadallah et al., 2020). Metabolic syndromes and neurological disorders are leading threats to public health and represent a global socioeconomic health burden. Available literature indicates that obesity, food restriction, and calorie control lead to depressive behavior and changes in the thought process. Ghrelin levels can minimize the stress-associated depression-like behaviors but may cause derangement in metabolic profile. Ghrelin also participates in the regulation of circadian rhythm. The intravenous injection of ghrelin for treatment of non-rapid eye movement (NREM) sleep, showed that it fosters sleep, although the effect varies for time and gender (Watson et al., 2012). Several human and animal studies postulated that intravenous administration of ghrelin increases the cortisol and aldosterone concentrations (Leggio et al., 2014). Night-time secretions of cortisol, growth hormone (GH), leptin, insulin-like hormone (ILH), follicle-stimulating hormone (FSH), and hypothalamic-pituitary-thyroid (HPT) hormones are persuaded by the ghrelin (Stone et al., 2020). Additionally, ghrelin shows a major action in cognition including learning and memory, which implies its involvement in the etiopathogenesis of central nervous system (CNS) disorders, especially manic disorder (Taran et al., 2014). Several study results from longitudinal aging revealed that a three-year follow-up study on old age patients showed positive enforcement of ghrelin in chronically ill depressive male patients (van Andel et al., 2022). Neurobiological mechanisms between depression, obesity, and anxiety have not been derived yet. However, the known increase in the comorbidity of anxiety and obesity may alter the feeding behavior, and subsequent depression (Shintani et al., 2001). An association between psychological disorders and increased visceral fat accumulation has been reported. Ghrelin has been a subject of many studies that focus on the pathophysiological mechanisms of appetite (Cummings et al., 2001; Patterson et al., 2011; Tschoep et al., 2001). Earlier research showed that ghrelin stimulates the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, hormone production and gene expression are both increased by ghrelin in the hypothalamus (Wittekind and Kluge, 2015; Ziko et al., 2018). A ghrelin-stimulated release of adrenocorticotropic hormone (ACTH) and cortisol has also been documented in animals (Kluge et al., 2013; Wittekind and Kluge, 2015; Wren et al., 2000). Additionally, it suppressed the release of hormones responsible for the hypothalamic-pituitary-gonadotrophic (HPG) axis, like LH (Kluge et al., 2007) and FSH (Kluge et al., 2009; Steiger et al., 2011). Ghrelin impacted the HPT axis in humans, producing an increase in thyroxine levels (Kluge et al., 2012).

The role of ghrelin in appetite regulation, cognition, emotions, and other psychological conditions has received attention for therapeutic manipulation using ghrelin in several pathologies, including obesity and depression (Schellekens et al., 2012). Ghrelin is also implicated in sleep and memory (Carlini et al., 2002). The characteristic episodes of depression are repeatedly conveyed by sleep disturbances, hunger, and memory alterations. These can be related to the involvement of ghrelin. Pharmacotherapy of depression has been evolving over the past few decades. The treatment approaches have been changing following our understanding of the disease pathophysiology. These treatment approaches also bring forth numerous limitations. Hence, following the recognition and establishment of ketamine as an antidepressant, there is a renewed interest in exploring monoaminergic pathways for the development of newer antidepressants (Morin et al., 2018). In the present review, we focused on the role of ghrelin in the regulation of neurosynaptic transmission in depressive disorders.

2. Methods

Several electronic search engines were used to conduct the literature review, including PubMed, Scopus, Science Direct, Web of Science, and Google Scholar. In the present review, all the authors separately conducted their literature searches. The eligibility criteria for inclusion of the articles in this review were clinical or pre-clinical findings reported in the English language.

3. Physiological roles of ghrelin

3.1. Ghrelin and depression

Although ghrelin is widely explored as a gut-derived appetite-stimulating hormone. It promotes food intake by stimulating neuronal activity of orexigenic NPY and agouti-related protein in the ARC (Chen et al., 2017). However, it is worth noting that ghrelin receptors are ubiquitously present in the CNS including in regions like the amygdala, hippocampus, nucleus accumbens, and ventral tegmental area (VTA) (Ferrini et al., 2009), which exhibit an essential role-play in the regulation of depression-related behaviors (Bali and Jaggi, 2015; Desai et al., 2014). Paradoxically, central ghrelin injection alleviates depression-like behavior triggered by prolonged unpredictable moderate stress (Huang et al., 2017). Besides the hypothalamus, ghrelin also regulates synaptic plasticity in neuronal circuits in the VTA and hippocampus, which can be correlated with its antidepressant effect (Serrenho et al., 2019). Viewed collectively, the available information suggests that in addition to orexigenic activity, ghrelin also produces an antidepressant effect by acting centrally.

Ghrelin is involved in many neurotransmission and signaling mechanisms in the brain. Several neurotransmitter systems are involved in the regulation of depressive disorders. The dopamineergic function of the brain is important in the control of mood and behavior related to the brain’s reward system. According to previously reported evidence, decreased levels of dopamine may elicit certain symptoms linked with depression (Belujon and Grace, 2017). Furthermore, earlier research indicated that ghrelin was prompted neuroprotection via the GHSR and promotes neuronal circuit activity related to learning and memory, as well as reward-seeking behavior. Ghrelin binds to substantia nigra pars compacta (SNpc) cells and electrically stimulates SNpc dopamine neurons, increasing tyrosine hydroxylase mRNA and dopamine levels in the dorsal striatum (Andrews et al., 2009). The research study also showed that in lipopolysaccharide-induced inflammation, ghrelin exhibits substantial inhibitory effects on proinflammatory cytokines such as interleukin 1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) (Ereg et al., 2019). Central administration of ghrelin increases dopamine release in the nucleus accumbens shell via activation of ghrelin receptors in the VTA, which may be causally linked with its antidepressant property. However, systemic treatment with ghrelin receptor antagonist JMV2959 prevented the ghrelin triggered dopamine release in the nucleus accumbens shell (Edvardsson et al., 2021). However, the particular mechanism for the involvement of ghrelin in manic disorders is not yet expanded or known, and diverse assumptions have been explored. The sedentary lifestyle is correlated with the problems of synthesis and metabolism of lipoproteins and different types of chylomicrons. In the depressed casualties, these changes were more pronounced and it is supported by the decreased alliance between the lipoprotein expressions and appearance. The disturbances in mood and depression are significantly altered by changes in lifestyle-related factors like smoking, and alcoholism (Marazziti et al., 2014; van Reedt Dortland et al., 2010). Ghrelin shares normal pathophysiological systems and is also involved in the regulation of the hunger pattern.

3.2. Role of ghrelin

Ghrelin plays many vital roles and regulates different functions. It is a quick-progressing hormone that is assumed to be involved in yearning and hunger. Ghrelin is secreted in early fetal development and promotes lung growth (Steculorum and Bontest, 2011). This discovery is important to a method known as “neurotrophic,” which refers to the memory’s ability to learn and adapt to new situations. Ghrelin, according to research, enters the hippocampus via the circulation and controls nerve-cell connections to improve learning and memory. Ghrelin levels are greater when the stomach is empty, making learning easier (Chen et al., 2009). Ghrelin has appeared to assume a role in the prevention of
unhappiness and nervousness. Mice inadequate in ghrelin have additionally appeared to display social shirking (Wittekind and Kluge, 2015). The different roles and functions of ghrelin are depicted in Fig. 1.

Ghrelin has endocrine, paracrine, or autocrine characteristics. Previous research also shows that a low level of ghrelin induces sleep with a significant improvement in sleep time (García-García et al., 2014). Ghrelin is also known to stimulate several hormones from the pituitary gland (Takaya et al., 2000). If the parallel nerve center is expelled (as found in rodents considers), taking care of it turns out to be less successive, prompting serious weight reduction and passing. On the off chance that the ventromedial nerve center is evacuated, taking care of expanding prompting weight gain and serious heftiness (Tsop et al., 2001). Ghrelin and its receptors are likewise found in the heart and the aorta (Mao et al., 2014). It, also, appeared to repress insulin emission in certain examinations (Wierup et al., 2004).

Ghrelin is involved in the molecular mechanisms in the brain and also mediates the various functions in the nervous system. In a depressed state, neurogenesis reduces the level of BDNF while increasing the concentration of cortisol above the normal level. The level of CREB is also decreased, followed by changes in behavior and an increased depressive state (Oh et al., 2006; Wang and Mao, 2019). Ghrelin stimulates GHS-R in vagal afferent nerve fibers in the stomach, resulting in the VTA and projected dopaminergic (mesolimbic) pathways, which in turn to, activation of the dopaminergic region and an increase in the BDNF level, ultimately CREB level is also increased and relieves the depressive symptoms and mood (Abizaid et al., 2006; Jerlhag et al., 2007; Skibicka et al., 2012). Several animal studies also revealed that ghrelin improves cognitive function via activation of the cAMP- CREB signaling pathway (Li et al., 2021). Furthermore, a recent line of investigation suggested that ghrelin is involved in neuronal morphogenesis via modulation of CREB levels in the damaged nerve by neurite outgrowth process formation (Stoyanova and Lutz, 2021) (Fig. 2). Recent studies have indicated that ghrelin administration causes dendritic spine remodeling in the hippocampus, and increases the production of certain BDNF-mRNA species (Perea Vega et al., 2021). Increased BDNF in dopamine-dependent VTA to dopamine-sensitive nucleus accumbens (NAc) leads to the anti-depressant activity with the help of transcription factor CREB by phosphorylation (Pittenger and Duman, 2008; Rubé et al., 2007). Several preliminary investigations have shown that patients with functional dyspepsia have increased expression of GDNF (Choi et al., 2021).

Fig. 1. Biological functions of ghrelin on different body systems.
et al., 2017). Moreover, a few studies have also postulated that increased expression of GDNF leads to activation of Pax 6, which leads to inhibiting the expression of ghrelin and somatotrophin, and glucagon (Rozanska et al., 2020).

Most of the studies have demonstrated the anti-depressive mechanisms of ghrelin. However, a few studies reported a negative impact as ghrelin itself produces depressive behavior and patterns in animals. Previously, it was reported that an increased level of ghrelin in animals could be because of calorie restriction. Chronic social defeat stress (CSDS), is when social stress induces depressive-like symptoms (Chuang et al., 2010). The GHSR-1 knockout mice demonstrated significantly increased depression-like behavior in response to CSDS (Walker, 2014). Delivery of a neuroprotective agent that increased neurogenesis and had significant antidepressant efficacy (Walker, 2014). A reduction in depression and related behaviors confirm the involvement of ghrelin with GHSR-1 activation (Serrenho et al., 2019).

Acute treatment of ghrelin in mice is shown to have anti-depressant properties (Carlini et al., 2002). The anti-depressant effect of ghrelin was shown to decrease gene expression and arginine vasopressin (AVP) levels in plasma, which suggests the antidepressant effect was partly via expression of AVP (Poretti et al., 2016). Ultimately, ghrelin appeared to increase noradrenergic (Carlini et al., 2002) transmissions similar to serotonergic transmission (Skibicka et al., 2012). Hence, adrenergic and serotonergic activation would be responsible for its anti-depressant effect (Jean and Kim, 2016). On the other hand, two examinations suggest the depressogenic properties of ghrelin (Skibicka et al., 2012). Long-term administration of ghrelin for more than about a month in rodents was related to a reduction of serotonin activity in the raphe nuclei (Skibicka et al., 2012). Ghrelin anti-sense DNA injection in the lateral ventricle of rodents actuated stimulants like impacts (Kanehisa et al., 2006). It has been found that ghrelin is detected in the patients having major depressive disorder (MDD) (Sorri et al., 2018), elevated (Esel et al., 2011), and equivalent, individually (Kurt et al., 2007; Matsuo et al., 2012). Depressive symptoms in healthy people brought about by catecholamine exhaustion were related to decreased ghrelin plasma levels (Cabral et al., 2012; Homan et al., 2013). It is suggested that inhibiting the body's response to ghrelin signals might be one method to help weight control by decreasing nourishment and increasing vitality. However, the above study explored that interruption of ghrelin signaling, might increase anxiety and depression (Zigman and Elmquist, 2003).

Remarkably, variations in estrogen levels may have a role in depressive-like behavior in postpartum females with oscillations inside the brain's BDNF-related components. Protein regulators of inflammation (BDNF and cytokines) are known to drive several intracellular signaling pathways linked to neuropsychological illness. Research studies suggested that patients with cancer and/or autoimmune diseases might be more likely to experience depressive symptoms due to pro-inflammatory cytokines (Numakawa et al., 2014). The GDNF protein and mRNA expression in the serum and hippocampus of depressive people have been shown to be decreased according to the findings in the former study (Lin and Tseng, 2015), which points to the importance of GDNF in the development of depression. The ghrelin affects mood and restricted the food intake of laboratory mice. The modified mice showed essentially more prominent social shirking than their wild-type partners, demonstrating a fuel of depression-like symptoms. Calorie limitation and losing weight could have an antidepressant effect and could be strengthening this illness, In future examinations, it needs to figure out which territory in the brain ghrelin causes these antidepressant-like effects (Chuang and Zigman, 2010). The previously reported studies have shown a reduced level of ghrelin in the sadness (Gecici et al., 2005; Gueler et al., 2007). Many studies have shown that the extent of ghrelin can not be comparable in normal and depressive patients (Ozsoy et al., 2014). The MDD is a severe mental condition characterized by weight loss, trouble sleeping, and tiredness with diminished physical capacity (Mischoulon et al., 2011). MDD pathophysiology is linked to HPA axis malfunction, abnormalities in the immune system, and alterations in monoamine receptors (De Kloet et al., 2005). Recent research has found that various energy-regulated hormones, such as Nesfatin-1 and ghrelin, exhibit endocrine disruptions in MDD patients (Açıkel et al., 2021; Ari et al., 2011; Bloem et al., 2012; Karadeniz et al., 2020). Ghrelin and Nesfatin-1 are recognized for antagonistically altering hormones, and they are linked to the seriousness of the illness. Patients' expectations and the efficacy of medications may also be affected by nesfatin-1 (Açıkel et al., 2021) and ghrelin levels (Hosoda et al., 2000; Nonogaki et al., 2008; Yosten and Samson, 2009).

4. Ghrelin variants and isoforms

Many isoforms of ghrelin are available like octanoylated ghrelin and diacyl ghrelin (Ferré et al., 2019). The ghrelin gene locus has been complicated by the presence of antisense transcripts, called ghrelin-OS (ghrelin opposite strand), in addition to producing multiple sense transcripts (Seim et al., 2007). The functional importance of these transcripts is still to be determined. Exon 3-erased preproghrelin, when
5.1. Ghrelin, agouti-related peptide (AgRP) and NPY

Previous research data demonstrated the molecular action of ghrelin through its ability to modulate the GHSR-1a receptor. It is mostly found in the hypothalamic neurons of the brain that express NPY and AgRP (Narayanaswami, 2012). The implications of ghrelin ligands, on the other hand, demonstrate that ghrelin-induced hunger and gain in body weight do not appear to occur (Schmid et al., 2005). Furthermore, it is being investigated if anorectic actions of NPY-Y1 antagonists or opposing molecular pathways in genetically engineered mice contribute to this evident alteration (Schmid et al., 2005). Subsequent investigations demonstrate that ghrelin triggers stronger AgRP mRNA activity than NPY mRNA, suggesting the highest impact of ghrelin through receptors of the melanocortin system (Cone, 2005). According to a recent study, ghrelin's effects on energy balance are mediated by the CNS and regulated by the PPARγ Control (Castañeda et al., 2010). Ghrelin activity is associated with both the CNS and the melanocortin mechanism (Dietrich et al., 2010).

5.2. Ghrelin and blood-brain barrier (BBB)

There is no definitive evidence to support ghrelin's presence in the brain's GHS-1a receptors. Many studies have also suggested that ghrelin could have connections to its receptor through circumventricular organs such as the median eminence. Some investigations also demonstrate that in the presence of a less protected BBB, ghrelin enters the ARC directly (Banks et al., 2008). In ARC, GHSR-1a expressing neurons (NPY/AGRP) demonstrate that ghrelin triggers stronger AgRP mRNA activity than NPY mRNA, suggesting the highest impact of ghrelin through receptors of the melanocortin system (Cone, 2005). According to a recent study, ghrelin's effects on energy balance are mediated by the CNS and regulated by the PPARγ Control (Castañeda et al., 2010). Ghrelin activity is associated with both the CNS and the melanocortin mechanism (Dietrich et al., 2010).

### Fig. 3. Involvement of ghrelin in different signaling pathways and its physiological roles in impacting the different situations.

- **Ghrelin**
  - Signaling Pathways
  - Physiological Roles
  - Apoptosis
  - Invasion
  - Angiogenesis
  - Proliferation
  - Inflammation
  - Growth Hormone
  - Cardiac Function
  - Metabolism

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that acrylate ghrelin may play a less important role than de-acrylate pancreatic islets may not express GHSR-1a, but human islets do, implying calcium via the adenylate cyclase of the body’s numerous activities. In the rat ARC, ghrelin increases cal-

5.4. GHSR-1a intracellular signaling system

The regulation of GHSR-1a is also an important aspect of the control of the body’s numerous activities. In the rat ARC, ghrelin increases calcium via the adenylyl cyclase – protein kinase A (AC – PKA) pathway. Calcium is one of the most common signaling modes employed by GHSR-1a receptors. In GHSR-1a cells, calcium has been found as a key biomarker for detecting ghrelin. Ghrelin tends to initiate signal transduction that leads to the development of food intake control. Ghrelin regulates the inner workings of cells via regulating GI and inflammatory cytokines (Camina, 2006). Recent research suggests that fatty acid production, AMPK activation, and ultimately oxygen radicals with endoplasmic reticular stress in the ARC and ventromedial hypothalamus may further increase ghrelin’s orexigenic function. Ghrelin can also inhibit proinflammatory cytokines by activating calmodulin-dependent kinase (CaMKK) and endothelial nitric oxide synthase (eNOS). By boosting ghrelin levels and decreasing fatty acid synthesis activity in the hypothalamus, ghrelin has been demonstrated to promote fasting food intake (Xu et al., 2008).

The hypothalamus and pituitary gland have the most GHSR-1a receptors, whereas the hippocampus, midbrain, and hindbrain have the least. GHSR-1b, a shorter version of the receptor arising from alternative gene splicing, exists but does not bind ghrelin. Additionally, GHSR-1a receptors can also be present in vagal and spinal visceral afferents, immunological cells, thyroid, pancreas, spleen, cardiac muscle, ovarian, and adrenal tissue, among other tissues (Yin et al., 2014). Human myocytes were shown to have growth hormone-releasing peptide (GHRP) binding sites. Such a receptor was accidently recognized as CD36, a glycoprotein IV membrane with a far lower affinity for native ghrelin than GHRPs. Several in-vitro investigations examined available facts for the next peripheral ghrelin receptor that affects obesity (Wiedmer et al., 2007). According to the findings, ghrelin receptors may have an important yet undiscovered role in paracrine pancreatic activities. It is also known to trigger 3T3-L1 pre-adipocyte development and to bind directly with a high affinity to non-GHSR-1a cells. Aside from that, mouse pancreatic islets may not express GHSR-1a, but human islets do, implying that acylate ghrelin may play a less important role than de-acylate ghrelin. The relationship between acylated and non-acylated kinds of ghrelin has also been shown, mostly in human thyroid and breast cancers. A large quantity of indirect information suggests the presence of functionally relevant non-GHSR-1a ghrelin receptor types (Delhanty et al., 2013). Long-term injection of ghrelin as an anorexigenic peptide has been shown in studies to promote and accelerate weight gain by increasing food consumption and decreasing energy expenses (Misra, 2013). It is known to have GHS-R agonist activity, which is controlled peripherally and directly in the brain, and it generates a feed reaction as well as a decrease in NPY levels (Wren et al., 2000).

The hyperphagic properties of ghrelin are generally linked to brain activity, with a special emphasis on the characterization of key processes related to ghrelin-driven excessive intake. The study was primarily concerned with locating the GHS-R within the feed-related circuitry of the hypothalamus region (Olszewski et al., 2008). This adaptive inter-

6. Central actions of ghrelin

6.1. Ghrelin and neurodegenerative diseases

Previous data postulated the neuroprotective role of ghrelin, soon after its discovery (Frago et al., 2011). However, a huge body of evidence has accumulated, which affirms this perception as well as unequivocally proposes a role of ghrelin in neurogenesis, neural versatility, learning, memory, and neurodegenerative diseases, most notably Alzheimer’s disease (AD) (Bayliss and Andrews, 2013; Walker, 2014). Researchers discovered that ghrelin reduces the toxicity of amyloid beta (Aβ)-oligomers by lowering superoxide levels and modulating mitochondrial metabolism in brain cells (Wittekind and Kluge, 2015). Distantly administered Aβ was demonstrated to exacerbates cognitive impairment and neurodegeneration in the hippocampus in the AD animal model (Moon et al., 2009; Nakhate et al., 2018, 2020). Ghrelin receptors are found throughout the CNS, most notably in the hypothalamus, pituitary gland, hippocampus, VTA, and amygdala (Mortazaei et al., 2019; Spencer et al., 2015).

The discoveries of most of the studies are consistent, recommending the memory-improving and neurogetic impact of ghrelin as determined underneath. Ghrelin has been proven to have cognitive effects, notably in the hippocampus, a region of the brain important for cognitive growth and learning. Ghrelin, for example, would have the choice of penetrating the blood-brain barrier and boosting dendritic spine neuronal assimilation and also long-term stimulatory effects in mice (Diano et al., 2006). Furthermore, recent research has demonstrated that ghrelin can induce hippocampus neurogenesis in both in-vitro and in-vivo tests (Walker, 2014; Zhao et al., 2007). The relevance of these observations is enhanced by the fact that ghrelin has consistently been shown to improve memory performance and spatial learning in animal models (Babri et al., 2013). Except for one study that found a memory-impairing impact of ghrelin (Zhao et al., 2014). Human trials are rare, and the results have been conflicting. Ghrelin serum concentrations have been demonstrated to be both positively connected with verbal learning (Belzar et al., 2013), and adversely correlated with verbal learning and other cognitive functions (Zubieta et al., 2001).

Even the placebo-controlled analysis of the effect of ghrelin on the midnight development of motor development did not establish important comparisons between ghrelin and the placebo-controlled condition (Allas et al., 2018). More efficient and reliable investigations are expected to additionally explain the connection between serum ghrelin levels and memory execution in humans. Other later in vitro investigations depicted cell-defensive properties (Wittekind and Kluge, 2015). Ghrelin and
ghrelin agonists were also shown to be viable in another animal model of dementia, demonstrating hippocampus neurogenesis (Bayliss et al., 2016; Moon et al., 2009). A team of researchers discovered that peripherally administered ghrelin can reactivate hippocampus neurogenesis (Li et al., 2013). As a result, ghrelin offers neuroprotection without calorie restriction (Bayliss et al., 2016).

The most recent study has shed fresh insight on the several molecular pathways by which ghrelin exerts its neuroprotective and anti-apoptotic actions. Mitochondrial dysfunction has also been involved in dementia pathways by which ghrelin exerts its neuroprotective and anti-apoptotic actions. Mitochondrial dysfunction has also been involved in dementia (Ma et al., 2014; Morgan et al., 2018). Several investigations have suggested that the phosphatidylinositol-3-kinase enzyme is involved (PI3K) (Chen et al., 2011; Lim et al., 2011). Different systems are likely included in the balance of neurotrophic factors (Stoyanova, 2014) and extracellular signal managed kinase (ERK 1/2) (Chen et al., 2011; Chung et al., 2008). In line with the findings of animal models, ghrelin mRNA production was shown to be lower in three separate areas of the temporal gyrus in human patients with AD compared to unaffected healthy controls in a post-mortem examination (Gahete et al., 2010). Fasting ghrelin blood levels in 14 patients and 14 healthy individuals, categorized by body mass index and age, did not differ significantly in cross-sectional research (Fig. 4, Table 1) (Stylianou et al., 2007).

6.2. Ghrelin in addictive disorders

It is realized that ghrelin is released at the time of a nutrition deficit and increases the consumption of calories. There has been considerable evidence that ghrelin is needed to mediate the motivation and reinforcing impact of amenable food in both animals and humans (Chuang et al., 2011; Egecioglu et al., 2011). This hypothesis supports the phenomenon of stress feeding as well as the belief that ghrelin interferes with stress-induced particular food in mice (Chuang et al., 2011). The craving for drugs and substance abuse are associated with the hyperactivation of the central ghrelin system (Zallar et al., 2017). A recent study reveals that the endogenous ghrelin system, which may be regulated and targeted to minimize the consequences of cocaine use, as it plays a substantial role in cocaine addiction (You et al., 2021). In addition, a robust correlation between neural pathways governing food and drug incentives has frequently been proposed (Volkow et al., 2011), and the outcomes of human and animal experiments include endocrine in diet and medication rewards. GHSR-1a-knockout mice did not show an improvement in the monoamine neurotransmitter produced inside the NAc, an essential aspect of a specific brain mechanism that was often uncovered with appetizing food (Egecioglu et al., 2011). Moreover, central and general administration of endocrine caused a monoamine neurotransmitter to uncheck within the nucleus accumbens in rodents (Abizaid et al., 2006; Jerlhag and Engel, 2011; Quarta et al., 2009). Comparatively, endocrine injections in humans were correlated with greater stimulation of reward and recognition structures (VTA, amygdala, anterior insula, orbitofrontal cortex) than placebo injections in the correlated grade fMRI research conducted on neural reaction to food video (Malik et al., 2008).

The trigger was shown to be positively associated with self-reported starvation levels. Surprisingly, ghrelin enhanced responsiveness in brain areas involved in attention and memory, as well as food memory (Malik et al., 2008). In addition, GABAergic transmission has consistently been shown to be implicated in alcohol consumption (Cruz et al., 2013). Crucially, the actions of ghrelin on the release of dopamine are regulated by GHSR-1a. At that point, no results have been observed if GHSR-1a has been antagonized (Abizaid et al., 2006; Jerlhag and Engel, 2011). Several neurological and neuropsychiatric disorders have been linked to the NMDA receptor, including AD (Liu et al., 2019), depressive disorder, anxiety, and addiction (Parsons et al., 1998). Moreover, a few studies have suggested that excessive glutamate and consequent overstimulation of NMDA receptors, resulting in excessive Ca2+ influx, are involved in the pathogenesis of several neurodegenerative disorders (Mody and MacDonald, 1995; Sattler and Tymianski, 2000).

Antagonism of the NMDA receptor even lessened the production of ghrelin-induced dopamine in the VTA, a brain rewarding system, indicating the presence of the glutamatergic system (Jerlhag and Engel, 2011). This can be relevant, as this technique is thought to be concerned with the manifestation of habit-forming disorders (Ross and Peselow, 2009), and is hypothesized to possess indications of depressive disorders (Bahi et al., 2013). Surprisingly, endocrine also increased reaction in brain regions involved in attention and memory, resulting in enhanced recollection of food footage. Antagonism of the NMDA receptor additionally dulled ghrelin-induced monoamine neurotransmitter unleash within the VTA, Some main structure inside the brain reward system, which indicates the presence of the glutamatergic system (Jerlhag and Engel, 2011). This can be of significance, as this technique is thought to be related to the looks of habit-forming disorders (Ross and Peselow, 2009), and is calculable to possess signed in spectacular disorders (Pilc et al., 2013). However, endocrine influences the development of fixation,
Table 1

| Central Effects of Ghrelin | Alzheimer’s disease | Addictive disorders | Stress and Anxiety | Schizophrenia | Parkinson’s disease |
|---------------------------|---------------------|---------------------|--------------------|--------------|--------------------|
| **Ghrelin mRNA, Acylated ghrelin** | | | | | |
| **Neuropeptide Receptors** | GHS-R1a, GHS-R1b | GHS-R1a | | | |
| **Hippocampus, NPY cells, ARC** | | | | | |
| **CNS** | | | | | |
| **Temporal gyrus, Amygdala, Orbitofrontal cortex, Amygdala, Hippocampus, Subgenual system** | | | | | |
| **Type of Model** | AD and MCI Patient | GHS-R1a-KO mice | | | |
| **Molecular Pathways** | GSPR3a, GSPR3b | | | | |
| **AD and MCI Patient** | | | | | |
| **References** | Roybal and Andrews, 2013; Walker, 2014 | Chang et al., 2011; Cruz et al., 2012; Walker, 2014 | | | |

### 6.3. Ghrelin and neuropsychiatric conditions

#### 6.3.1. Ghrelin in schizophrenia

Schizophrenia is related to an elevated level of psychological stress. Adjustments in the ghrelin framework appear to be good and beneficial (Lodge and Grace, 2011). Investigations looking at ghrelin levels in schizophrenics and stable controls have found that ghrelin levels in schizophrenics were substantially greater (Palik et al., 2005) with one examination finding decreased serum levels of ghrelin (Togo et al., 2004). Many studies have shown the impact of an antipsychotic drug on ghrelin levels (Togo et al., 2004). While a few examinations propose an expansion of ghrelin because of treatment with atypical antipsychotics (Esen-Danaci et al., 2008; Sentissi et al., 2009) others find no distinction (Himmerich et al., 2005) or abatement in ghrelin levels (Tanaka et al., 2008; Wysokiński et al., 2014). Curiously, antipsychotics found increased ghrelin in patients who experienced a weight gain (Jin et al., 2008), perhaps suggesting a disturbance of the negative criticism instrument of ghrelin emission.

#### 6.3.2. Ghrelin and stress

Numerous findings from human and animal studies point to ghrelin’s critical involvement in stress response regulation. The neural circuits that regulate anxiety are essentially connected to those that regulate mood, fear, and anxiety. It has been suggested that the hippocampus, the amygdala, a paraventricular thalamic nucleus, and the hypothalamic system to be specific to its role in tailored learning. Likewise, discoveries from a miscellany assortment of animals ponder to demonstrate that endocrine is related to the pathological process of addiction: endocrine receptor threat attenuated operative organization of alcohol and high alcohol utilization in rodents (Kaur and Ryabinin, 2010).

Previously, endocrine knockout mice have demonstrated slightly less voluntary alcohol intake than wild mice (Bahi et al., 2013). The report postulated that ghrelin antagonism reduced alcohol consumption and locomotor operation in wild mice (Bahi et al., 2013). Furthermore, ghrelin antagonism reduced alcohol intake in rats after 2, 5, and 10 months of active alcohol consumption, as well as the effects of alcohol deprivation and relapse in alcohol consumption (Suchankova et al., 2013). The effects of psychostimulant cocaine have shown similar results. Following the fundamental organization of ghrelin and cocaine and compared with cocaine alone, rats showed improved locomotor movement and conditioned place inclination (Zambrana-Infantes et al., 2018).

A focal mixture of ghrelin prompted improved self-organization of heroin and upgraded heroin looking for conduct (Maric et al., 2012), and expanded dopaminergic transmission brought about by nicotine (Palotai et al., 2015). In people, dieting of serum ghrelin in early cellulose alcohol subordinate patients was raised contrasted with solid controls. The amount of alcohol consumed before forbearance was shown to be inversely related, but the time of restraint was found to be strongly related to ghrelin serum levels after restraint (Kim et al., 2005). Alcohol was additionally systematically shown to lower the endocrine body fluid levels (Zimmermann et al., 2007). Various studies have also shown that ghrelin levels were low before drinking discontinuation and increased significantly after the start of patience (Leggio et al., 2012). As a result, it has been consistently stated that ghrelin serum concentrations have been positively linked with alcohol. In addition, a new study has shown that inner secretion would elevate the appetite for alcohol.

This effect has not been discovered on the will to drink juice or eat food (Leggio et al., 2014). Two recent studies have also suggested that ghrelin may have a role in human nicotine addiction. It was found that a higher level of ghrelin in the initial 24–48 h after smoking ends was related to expanded wanting and danger of smoking backslide following a month (al’Absi et al., 2014). Another study revealed that intrauterine introduction to tobacco smoke was related to expanded ghrelin levels in adulthood, featuring the solid connection of the ghrelin framework with addictive substances (Paslakis et al., 2014) (Fig. 4).
structures are involved in the regulation of tension control (Hsu et al., 2014). As a result, a change in the brain circuits that govern pressure is likely to affect temperament and behavior. It was revealed by the selection of neurobiological mechanisms that paved the way for survival by controlling the response to environmental threats by incorporating changes in behavior, such as anxiety, mood, and feeding patterns (Bowers et al., 2014; Fittzsimons et al., 2019). In support of that one, the use of ghrelin usually induces an improvement in HPA (stress axis) hormone. A few studies indicate that the modulation of the HPA axis is linked to a difference in the amount of ghrelin (Azzam et al., 2017; Holubova et al., 2016). Previous research has demonstrated that adrenalextract results in greater fear learning and increased endogenous ghrelin in the stress response, indicating a stress response that is independent of the HPA axis (Meyer et al., 2014).

In a sequence of elegant studies with rats, it was shown that enhanced GHSR-1a-receptor activation was adequate and essential for increased fear (Bautwal et al., 2019). Systemic injection of the ghrelin receptor agonist improved the memory of anxiety but did not improve the corticotropin-releasing factor encouraging the authors to propose that ghrelin is involved in a novel aspect of the stress response (Meyer et al., 2014). Existing information powerfully showed an ascent of ghrelin serum levels after the presentation of psychological stress in both rodents (Lutter et al., 2008), and people (Ozsoy et al., 2014). Following that, women who revealed a significant number of relational stressors had greater blood ghrelin levels than those who revealed few or no relational stressors (Jaremka et al., 2015). By decreasing blood pressure and enhancing muscle responsiveness to mental stress, ghrelin affects a person’s physiological response to stress (Lambert et al., 2011). Even so, the effects of ghrelin are dependent on GH in the amygdala. Treatment with ghrelin and dietary restriction caused anxious-like symptoms in the elevated plus-maze. However, GHSR-1a-knockout mice showed no anxious-like effects, even when anxious-like-like effects were seen in all wild mouse models. Anxious-like symptoms were also observed in another study following an amygda infusion of ghrelin. Intriguingly, eating between both the infusion of ghrelin and the fear test prevents these anxious-like effects (Alvarez-Crespo et al., 2012). These discoveries let authors speculate that the elevation of ghrelin because of yearning prompts, a feeding response, however, if no food is accessible, it could be beneficial for endurance if anxiety-like behaviors that would somehow way or another cut off the rodents from discovering food were put out (Alvarez-Crespo et al., 2012). Several studies in unstressed rodents (Gaston et al., 2017) promote the anxiogenic activity of ghrelin. Ghrelin, on the other hand, has been linked to increased anxiety-like activity and fear memory following chronic stress. This study found that fear memory decreased in response to intense stress, suggesting that anxious-like effects are associated with ghrelin (Meyer et al., 2014). By doing so, ghrelin may exert anxious-like effects under high pressure while advancing anxiogenic activity under unstressed and constantly focused conditions.

The contradictory findings regarding the function of ghrelin in anxiety were not readily remedied. The concept that ghrelin has a dual impact, that it may be anxiogenic or anxious-like depending on the conditions, might explain some but not all the contradictory evidence (Meyer et al., 2014; Spencer et al., 2012). Ghrelin’s consequences for rest rely upon the method for an organization with a rest weakening impact after central administration (Szentirmai et al., 2009) and a rest improving impact after peripheral administration (Kluge et al., 2007). Moreover, there is some proof that ghrelin has various impacts depending on the site of its administration in the CNS (Gaston et al., 2017). Furthermore, the prior study did not reveal a link between panic disorder and ghrelin content polymorphism (Hansen et al., 2015; Nakashima et al., 2008).

6.3.3. Ghrelin and insomnia

Ghrelin is also, reported to have an essential role in a sleeping disorder. The nocturnal level of ghrelin in 14 men experiencing a sleeping disorder (Motivala et al., 2009). The sleeping disorder patients indicated fundamentally lower nighttime ghrelin levels. This outcome follows the predictable finding that ghrelin increases males’ rest. Deep sleep or non-REM sleep-promoting effects have been observed in teenagers (Schmid et al., 2006), elderly men (Kluge et al., 2009), and depressed men (Steiger et al., 2011). Conversely, ghrelin didn’t essentially influence sleep in youth (Kluge et al., 2007) old or depressed (Kluge et al., 2013) females. In men, intense lack of sleep was related to diminished nocturnal ghrelin plasma levels (Dzaja et al., 2004). Similarly, the plasma levels of ghrelin would be higher in the night following sleep deprivation than in the night preceding the sleep deprivation, suggesting a rest-improving effect (Schussler et al., 2006). Although ghrelin concentrations were shown to decrease throughout insomnia or sleep deprivation. The plasma concentration of ghrelin following a reduction in sleep is best correlated with the finding that chronic insomnia is related to obesity (Schmid et al., 2008; Spiegel et al., 2004; Taheri et al., 2004).

6.3.4. Ghrelin and Parkinson’s disease (PD)

PD is a common and disabling age-related mammalian neurodegenerative disorder characterized by the gradual depletion of dopaminergic neurons in the nigro pars compacts (SNc) of the midbrain, the presence of Lewy’s body lesions, and the deterioration of transmitting nerve fibers throughout the striatum. Such characteristics of the condition manifest in a variety of motor impairments, like fatigue, sitting tremors, posture dysfunction, and postural instability. In comparison, PD patients exhibit evidence of non-symptoms in the early stage of the disease. These included gastrointestinal (GI) dysfunction, hyposmia, sleep disturbance, and depressive symptoms (Lee and Koh, 2015). Because the ghrelin receptor (GHS-R1a) mRNA is highly distributed across many dopaminergic pathways (Mani et al., 2016).

Ghrelin is essential for the signaling of dopamine. The central administration of ghrelin to the third ventricle causes a rapid rise in locomotive activity and dopamine overload in the nucleus accumbens, which is antagonized by the GHS-R1a antagonist (Jelhag et al., 2007; Jerlhag and Engel, 2011). Peripheral or intra-VTA ghrelin treatment can also contribute to a rise in the extracellular concentrations of accumbal dopamine and dopamine retention (Abizaid et al., 2006; Quarta et al., 2009). Accordingly, Jiang and colleagues were able to provide the first proof of the neuronal function of ghrelin in nigrostriatal dopamine signaling by co-expressing both GHR-R and dopamine receptor-1 (D1R) in the substantia nigra. Ghrelin activation of the GHR-R has been demonstrated to increase dopamine/D1R-induced cAMP aggregation (Jiang et al., 2008). Because dopamine activity decreases during Parkinson’s disease pathology, the augmentation of D1R signaling following ghrelin therapy ensures that ghrelin can counteract the amplification of dopamine activity. As a result, several researchers showed that ghrelin might suppress the dopamine nigrostriatal pathway in several Parkinson’s disease models (Andrews et al., 2009; Jiang et al., 2008; Moon et al., 2009). Till now, the majority of ghrelin-induced PD research has examined neuroprotective effects on the nigrostriatal mechanism, neurophysiological regulation of nigral dopaminergic neurons, and nonmotor manifestations of the disorder (Table 1).

6.3.5. Ghrelin and neuroprotection via nigrostriatal system

GHS-R1a is frequently found in dopaminergic nerve signals. Ghrelin has been demonstrated to counteract both dopaminergic neuron deficits in the SNc and dopamine decrease in the striatum. These findings were mediated by GHS-R1a since pretreatment with GHS-R1a antagonist (D-Lys3-GHRP-6) eliminated ghrelin’s impact (Jiang et al., 2008). This finding was supported by investigations into numerous MPTP-induced PD in animal models in which animals with PD rescue characteristics were also eliminated through D-Lys3-GHRP-6 administration or GHS-R1a knockout (Andrews et al., 2009; Moon et al., 2009). Ghrelin offers neuroprotection via mitochondrial activity and microglial activation. This group includes apoptotic pathways related to mitochondria, oxidative stress, and mitochondrial biogenesis. The effect of ghrelin on MPTP-induced apoptosis was previously demonstrated by an increased Bax/Bcl-2 ratio and repression of apoptosis induction by ghrelin.
treatment (Dong et al., 2009; Jiang et al., 2008; Van Kaer, 2011). This is similar to previous cases of focal cerebral ischemia/reperfusion damage. Ghrelin improved mitochondrial pattern is defined to require the stimulation of the uncoupling protein-2 (UCP2) which removes the effects of ghrelin (Andrews et al., 2009). It is important to remember that ghrelin-induced neuronal activity is not limited to SNc but also occurs in several other brain areas, including the hypothalamus and hippocampus (Abizaid et al., 2006). This indicates that UCP2 is the normal target of ghrelin neuroprotective effects.

It has been hypothesized that AMPK (5'-adenosine monophosphate-activated protein kinase) stimulation and increased mitophagy could also facilitate ghrelin regulation using mitochondrial biogenesis (Bayliss and Andrews, 2013). This hypothesis demands more proof. In PD, ghrelin has neuroprotective effects, including disabling microglia and reducing inflammation. Microglia activated by MPTP and inflammatory mediators such as TNF-5-007 and IL-1β are inhibited by ghrelin in the acute PD mouse model and also in cultures of main mesencephalic neuroglia (Moon et al., 2009).

CRediT authorship contribution statement

Milind V. Masule: Writing – original draft. Sumit Rathod: Writing – original draft. Yogesta Agrawal: Writing – original draft. Chandragouda R. Patil: Writing – review & editing. Kartik T. Nakbate: Writing – original draft. Shreesh Ojha: Writing – review & editing. Sameer N. Goyal: Conceptualization, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of Abbreviations

5-HT 5-Hydroxytryptamine
ACC Acetyl-CoA Carboxylase
ACTH Adrenocorticotropic Hormone
AD Alzheimer's disease
AGRP Agouti-Related Protein
Bax Bax-2-associated X protein
BBB Blood-Brain Barrier
Bcl-2 B-cell lymphoma 2
BDNF Brain-Derived Neurotrophic Factor
CaMK-II Ca2+ and Calmodulin-Dependent Protein Kinase II Pathway
CaMKK Calmodulin-Dependent Kinase
CAMP Cyclic Adenosine Monophosphate
CAMP/PKA cAMP-Dependent Protein Kinase
CAT Catalase
CD-36 Cluster of Differentiation 36
CNS Central Nervous System
CREB cAMP Response Element-Binding Protein
CRH Corticotrophin-Releasing Hormone
CSDS Chronic Social Defeat Stress
D1R Dopamine Receptor Subtype
DMH Dorosmedial Hypothalamic Nucleus
ECT Electroconvulsive Therapy
eNOS Endothelial Nitric Oxide Synthase
ERK1/2 Extracellular Sign Controlled Kinase 1/2
FAC Fatty Acid Synthase
FSH Follicle-Stimulating Hormone
GABA Gamma-Aminobutyric Acid
GDNF Glial Cell Line-Derived Neurotrophic Factor
GH Growth Hormone
GHSR Growth Hormone Secretagogue Receptor
GOAT Ghrelin O-Acyltransferase
GRB-2 Growth Factor Receptor-Bound Protein 2
GSK3β Glycogen Synthase Kinase 3 Beta
HDL High-Density Lipoprotein
HPA-axis Hypothalamic-Pituitary-Adrenal Axis
HPG axis Hypothalamic-Pituitary-Gonadal Axis
HPT axis Hypothalamic-Pituitary-Thyroid Axis
HYP Hypothalamus
IRS-1 Insulin Receptor Substrate 1
LDL Low-Density Lipoproteins
LH Luteinizing Hormone
MAPK Mitogen Initiated Protein Kinase
MDD Major Depressive Disorder
MPTP 1-Methyl-4-Phenyl-1, 2, 3, 6-Tetrahydropyridine
mRNA Messenger RNA
NAc Nucleus Accumbens
NF-kB Nuclear Factor Kappa-Light-Chain- B Cells
NMDA N-Methyl-D-Aspartate
NPY Neuropeptide Y
NREM Non-Rapid Eye Movement
NTS Nucleus of the Tractus Solitarius
p38 Mitogen-Activated Protein Kinases
PD Parkinson's disease
PFC Pre-Frontal Cortex
PI3K Phosphatidylinositol-3-Kinase
PKC Protein Kinase C
PLC-PCK Phospholipase C-Protein Kinase C
PPAR-γ Peroxisome Proliferator-Activated Receptor Gamma
ROS Reactive Oxygen Species
SNc Substantia Nigra Pars Compacta
SNP Single Nucleotide Polymorphisms
SOD Superoxide Dismutase
TNF-α Tumor Necrosis Factor Alpha
TSH Thyroid-Stimulating Hormone
UCP-2 Uncoupling Protein-2
VTA Ventral Tegmental Area

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