

Agomelatine: a potential novel approach for the treatment of memory disorder in neurodegenerative disease

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Abstract

Agomelatine is a selective agonist of melatonin receptor 1A/melatonin receptor 1B (MT₁/MT₂) and antagonist of 5-hydroxytryptamine 2C receptors. It is used clinically to treat major depressive episodes in adults. The pro-chronobiological activity of agomelatine reconstructs sleep-wake rhythms and normalizes circadian disturbances via its agonistic effect of melatonin receptor 1A/melatonin receptor 1B, which work simultaneously to counteract depression and anxiety disorder. Moreover, by antagonizing neocortical postsynaptic 5-hydroxytryptamine 2C receptors, agomelatine enhances the release of dopamine and noradrenaline in the prefrontal cortex, increases the activity of dopamine and noradrenaline, and thereby reduces depression and anxiety disorder. The combination of these two effects means that agomelatine exhibits a unique pharmacological role in the treatment of depression, anxiety, and disturbance of the circadian rhythm. Emotion and sleep are closely related to memory and cognitive function. Memory disorder is defined as any forms of memory abnormality, which is typically evident in a broad range of neurodegenerative diseases, including Alzheimer's disease. Memory impairment and cognitive impairment are common symptoms of neurodegenerative and psychiatric diseases. Therefore, whether agomelatine can improve memory and cognitive behaviors if used for alleviating depression and circadian-rhythm sleep disorders has become a research "hotspot". This review presents the latest findings on the effects of agomelatine in the treatment of psychologic and circadian-rhythm sleep disorders in clinical trials and animal experiments. Our review evaluates recent studies on treatment of memory impairment and cognitive impairment in neurodegenerative and psychiatric diseases.

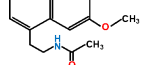
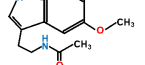
Key Words: agomelatine; antidepressant; anxiety; apathy; circadian-rhythm sleep disorder; cognitive impairment; depression; melatonergic; memory disorder; mood disorder; neurodegenerative disease

Introduction

Agomelatine (AGO) is N-(2-[7-methoxy-1-naphthalenyl]ethyl) acetamide (S20098). It was discovered and developed by the European Pharmaceutical Company Servier Laboratories Limited in 1992 (Yous et al., 1992; Armstrong et al., 1993). As the first melatonergic antidepressant, AGO was approved by the European Medicines Agency in the European Union in 2009 and Therapeutic Goods Administration in Australia in 2010 for the treatment of major depression. AGO alleviates circadian-rhythm sleep disorders in patients suffering from depression with synergistic agonism at melatonin receptor 1A/melatonin receptor 1B (MT₁/MT₂) and antagonism at 5-hydroxytryptamine 2C (5-HT_{2C}) receptors. AGO provides a useful alternative pharmacological strategy to existing antidepressant drugs (Norman and Olver, 2019).

Commonly used drugs for depression are selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), which ameliorate depression by increasing the 5-hydroxytryptamine (5-HT) level. However, SSRIs and SSNRIs produce adverse effects, such as withdrawal syndrome, sexual dysfunction, difficulties in sleeping, and agitation (Erdoğan et al., 2020). Compared with SSRIs and SSNRIs, AGO exerts an antidepressant effect by binding directly to 5-HT_{2C} receptors in postsynaptic membranes without affecting 5-HT concentrations in synaptic clefts. Furthermore, compared with natural endogenous melatonin, the replacement of an indole ring with a naphthalene ring in AGO (Table 1) enhances the metabolic stability of AGO and prolongs its biological half-life, which leads to more effective correction of circadian-rhythm disorders and alleviation of sleep disorders by activating MT₁ and MT₂. With synergistic agonism at MT₁/MT₂ and antagonism at 5-HT receptors, AGO has obvious positive effects on the sleep-wake cycle and depression while lacking serious side effects (including sexual side effects) (Kennedy et al., 2008).

Table 1 | Comparison of drug characteristics between agomelatine and melatonin

Drug name	Agomelatine	Melatonin
Source	Chemical synthesis	Endogenous hormone
Weight (kDa)	243	232
Half-life	< 2 h	35–50 min
Chemical formula	C ₁₅ H ₁₇ NO ₂	C ₁₃ H ₁₆ N ₂ O ₂
Chemical structure		
Pharmacological properties	Antagonist of 5-HT _{2C} receptors; agonist of MT ₁ and MT ₂	Agonist of MT ₁ and MT ₂

5-HT_{2C}: 5-Hydroxytryptamine 2C; MT₁: melatonin receptor 1A; MT₂: melatonin receptor 1B.

Neurodegenerative disease refers to the principal pathology associated with disorders such as Alzheimer's disease, Huntington's disease and Parkinson's disease. The patients with these diseases exhibit diverse patterns of sleep disturbance, memory disorder and cognitive impairment. Many researchers have reported a strong association among sleep disturbance, mood changes, memory complaints, and reduced cognitive performance (Tempesta et al., 2018; Guan et al., 2020; Gutierrez et al., 2021; Xie et al., 2021; Hernandez and Shukla, 2022). Sleep disorders, emotional abnormalities, and cognitive decline are usually present in the same individual and influence each other. An improvement in sleep and mood disorders often alleviates memory deficit and cognitive decline. Therefore, based on the peculiar characteristic of AGO

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integrating melatonergic agonism and 5-HT antagonism and the efficacy of AGO in improving sleep and mood, it is intriguing and meaningful to ascertain if AGO can also ameliorate the deficits in memory and cognitive behaviors while attenuating depression and sleep-rhythm disorders.

Here, we summarize the latest research progress of AGO in the treatment of depression, sleep disorders, and cognitive impairments. We aim to provide new insights into the pharmacological action and mechanisms of AGO in the clinical setting.

Search Strategy and Selection Criteria

The studies cited in this narrative review were published from 2000 to 2021. They were searched by QS and TL on 31 December 2021 using the PubMed database and met the inclusion criteria, search terms include at least one of the following keywords “agomelatine” and “S20098”, and at least one of the following keywords: “mood disorder”, “depression”, “anxiety”, “apathy”, “anhedonia”, “sleep-rhythm disorder”, “memory”, “cognition”, “dementia”, and “neurodegenerative disorder”.

Agomelatine and Mood Disorders

Mood disorders are a group of mental or psychiatric disorders, such as depression, anxiety and apathy, and are characterized by abnormalities of emotional state (Marshall, 2020). These emotional disorders have a negative impact on the physical and mental health of patients, and also impose a heavy burden on their families and society. According to Chisholm et al. (2016), depression and anxiety disorders cost the global economy USD1.15 trillion each year. AGO can improve depression, anxiety, apathy, and other mood disorders, especially major depressive disorder (MDD).

Depression

Depression (also known as depressive disorder) is one of the most common mood disorders, and is characterized by a persistent low mood state. The accompanying symptoms of depression include inactivity, loss of concentration, social withdrawal, sleep disturbances, and cognitive impairments, such as memory deficit (LeMoult and Gotlib, 2019; Price and Duman, 2020).

AGO is used mainly for the treatment of depression, especially MDD. Heun et al. (2013) undertook a study on 222 older patients with MDD. They found that AGO treatment for 8 weeks relieved depressive symptoms efficiently and was well tolerated in older patients suffering from depression (Heun et al., 2013). Similarly, Robillard et al. (2018) reported that AGO reduced depressive symptoms significantly in 24 young adults with depression. Moreover, they found that the timing of dim light melatonin onset (DLMO) was shifted 3.6-hour earlier after treatment with AGO, which indicated a strong correlation between the improvement of depression and the phase shift of DLMO (Robillard et al., 2018). In a network meta-analysis, Cipriani et al. (2018) reported that AGO was more efficacious and acceptable in adult patients with major depression than other antidepressants. Recently, a 1-year multicenter observational study in France showed that AGO improved the quality of life and daily functioning of MDD patients and alleviated depression-related functional disability, with good efficacy and tolerability noted during the treatment period (Gorwood et al., 2020). In an open evaluation, AGO treatment for over 14 weeks in 37 patients with acute depression and seasonal affective disorder led to 76% having a response and 70% achieving remission (Pjrek et al., 2007).

Bipolar disorder is a chronic episodic mental disorder characterized by intermittent episodes of depressive and manic symptoms (Post, 2005; Tondo et al., 2017). Long-term use of antidepressants can increase the risk of patients with depression suffering mania or hypomania. Hence, a combination of antidepressants and mood stabilizers (e.g., lithium or sodium valproate) is, in general, the main approach for treating bipolar disorder (Grunze et al., 2018). AGO, as an adjunctive treatment with lithium or sodium valproate, was evaluated in bipolar disorder and was found to be efficacious in alleviating the symptoms of the patients after 6-week treatment (Calabrese et al., 2007; Fornaro et al., 2013).

The mechanism of action of AGO in the treatment of depression is focused on the synergistic effects of AGO on activation of MT₁/MT₂ and antagonism of 5-HT_{2C} receptors. It has been reported that 90% of patients suffering from depression showed different degrees of sleep disorders (Tsunoo et al., 2005). The quality of sleep and the outcome of depression had a mutually causal relationship. Thus, improvement in sleep quality can directly alleviate the emotional status of patients suffering from depression. Activation of MT₁/MT₂ by AGO can improve the sleep quality and daytime wakefulness of patients which, in turn, attenuates depressive symptoms.

5-HT_{2C} receptors are the only known G protein-coupled receptors subjected to “RNA editing”, a mechanism which generates multiple variants of a particular gene product, thereby producing isoforms of 5-HT_{2C} receptors with various properties (i.e., affinity, coupling, and constitutive activity) (Werry et al., 2008; Schmauss et al., 2010). Weissmann et al. (2016) documented a marked increase in RNA editing on 5-HT_{2C} receptors in specific brain regions of patients who felt suicidal and depressed. Hence, region-specific changes in editing of the messenger-RNA of 5-HT_{2C} receptors and deficient receptor function likely contribute to the etiology of depressive disorder or suicidal ideation (Weissmann et al., 2016). Usually, 5-HT_{2C} receptors inhibit downstream release of dopamine and norepinephrine from some brain

regions (e.g., prefrontal cortex) involved in regulation of emotion (Alex and Pehek, 2007). Compared with SSRI antidepressants, the antidepressant and anti-anxiety effects of antidepressants are stronger if 5-HT_{2C} receptors are antagonized (Demireva et al., 2020). AGO can antagonize 5-HT_{2C} receptors effectively without influencing the activity of G protein-coupled receptors, and it can normalize signaling at 5-HT_{2C} sites by blocking the actions of agonists and inverse agonists, thereby returning activity to a baseline value (Werry et al., 2008). By antagonizing 5-HT_{2C} receptors, AGO can also disinhibit release of dopamine and norepinephrine in the prefrontal cortex, thereby contributing to the effects of antidepressants (Millan et al., 2003; Stahl, 2014). In addition, AGO has neuroprotective effects because it has been shown to improve neuronal plasticity in the rat brain (Calabrese et al., 2011; Dagyte et al., 2011), upregulate brain-derived neurotrophic factor (BDNF) expression in the prefrontal cortex and hippocampus (Yucel et al., 2016; Lu et al., 2018), and activate the extracellular signal-regulated kinase-protein kinase B-glycogen synthase kinase 3β (ERK-AKT-GSK3β) signaling pathway (Duda et al., 2020), which can help to ameliorate the depressive disorder.

The development of antidepressants is slow due to the complexity of the etiology and unclear pathogenesis of depression. However, converging evidence from clinical trials and animal experiments has shown that the unique antidepressant effects of AGO breakthrough the conventional-treatment concept of SSRI and SSNRI antidepressants to provide a new strategy for the treatment of depression. Nonetheless, the antidepressant pharmacological mechanism of AGO has not been elucidated.

Anxiety disorder

Anxiety disorder is a common clinical neurosis characterized by excessive and persistent worry, with vegetative symptoms such as headaches and gastrointestinal complaints. Studies have demonstrated that AGO exhibits a good anxiolytic effect and tolerability (Stein et al., 2017; Slee et al., 2019), with a stronger clinical response and earlier improvement of symptoms than those elicited by SSRIs or SSNRIs (Buoli et al., 2017). AGO alleviated social isolation-induced anxiety in rats effectively and reversed increased plasma levels of vasopressin (Harvey et al., 2019). Similar to depression, the pathogenesis of anxiety disorder is complex, and the anxiolytic mechanism of AGO is incompletely understood. Several studies have suggested that the anxiolytic effects of AGO are associated mainly with its antagonism of 5-HT_{2C} receptors (Sant’Ana et al., 2019; Demireva et al., 2020). The modulation of glutamate neurotransmission, anti-inflammatory action, antioxidant action, and correction of melatonin rhythms are also involved in the anxiolytic-like effects of AGO (Tchekalarova et al., 2018; Santos et al., 2019). Moreover, anxiety disorder and depression often accompany each other, and a similar pathogenesis may exist between them. Therefore, AGO may relieve anxiety disorder by improving depression, and *vice versa*.

Other emotional disorders

Apart from its antidepressant and anxiolytic properties, it has been suggested that AGO may exhibit special curative effects on particular neuropsychiatric symptoms, such as apathy, anhedonia, and abulia. Apathy is one of the most prevalent behavioral and psychological symptoms of dementia. Apathy is characterized by an insidious decline in motivation and goal-directed actions, which leads to reduced interest in social, recreational, occupational, and creative pursuits. Callegari and colleagues showed that AGO (but not melatonin) improved apathy in patients with frontotemporal dementia and was well-tolerated (Callegari et al., 2016). Moreover, an analysis of the literature showed that AGO had an obviously positive effect on the treatment of apathy in people suffering from dementia (Harrison et al., 2016). De Berardis et al. (2013) showed that AGO reversed escitalopram-induced apathy markedly in a patient with MDD. Whether used alone or in combination with acetyl-L-carnitine, AGO can alleviate apathy in older patients with mild or moderate depression (Gavrilova et al., 2015). Clinical studies suggest that AGO has potential for the treatment of apathy, but how it improves apathy merits further exploration.

Another prominent symptom of many neuropsychiatric disorders is anhedonia (loss of interest and pleasurable feelings in response to previously rewarding stimuli) (Husain and Roiser, 2018). Anhedonia is most notable in MDD and schizophrenia. A pooled analysis of an open clinical trial showed that AGO could improve depression and anhedonia in a broad range of patients suffering from depression (di Giannantonio et al., 2019). AGO has been shown to reverse anhedonia-like deficits in rats exposed to chronic constant light (Tchekalarova et al., 2018). How AGO improves anhedonia is not well understood, but it has been reported that treatment with AGO or an antagonist of 5-HT_{2C} receptors, SB242084, reversed the anhedonia-like state in mice with knockout of glutamate ionotropic receptor NMDA type subunit 2D (Yamamoto et al., 2017). Hence, antagonizing 5-HT_{2C} receptors may be a strategy for treating anhedonia. Importantly, anhedonia has also been linked to dysfunctions in the dopamine system, which plays a part in reward prediction, motivational arousal, and responsiveness to conditioned incentive stimuli (Tye et al., 2013). Chenu and collaborators (Chenu et al., 2013) reported that chronic administration of AGO for 14 days increased the number of spontaneously active dopamine neurons, the “burst” activity of dopamine neurons, the firing rate of 5-HT neurons in the dorsal-raphe nucleus, and tonic activation of postsynaptic 5-HT_{1A} receptors located in the hippocampus. Those findings suggest that AGO may be involved in modulation of dopamine release in anhedonia. Nevertheless, the therapeutic mechanism of action of AGO in apathy and anhedonia must be elucidated.

Agomelatine and Sleep Disorders

Sleep disorders are a group of conditions in which the normal sleep pattern or sleep behaviors are disturbed. Primary sleep disorders include insomnia, hypersomnia, early waking, circadian-rhythm disorders, parasomnias, sleep-related movement disorders, and sleep-related breathing disorders (Pavlova and Latreille, 2019). Sleep disorders bring heavy economic burdens to patients' families and society. Annual insomnia-related expenses have been estimated to be USD150–175 billion worldwide in 2016 (Reynolds and Ebben, 2017). Patients with psychiatric disorders and dementia have more severe sleep disorders which, in turn, contribute to earlier onset and more rapid progression of neurodegenerative disorders (Benca et al., 1992; Shi et al., 2018). Froböse et al. (2012) showed that a young patient with fatal familial insomnia had improved sleep efficiency, enhanced slow-wave sleep, and fewer awakenings during sleep periods after AGO treatment. In another study, AGO treatment for 6 months decreased the Depression Scale score significantly, and improved limb movements, sleep, and awakening significantly in patients suffering from depression and Parkinson's disease (Avila et al., 2015). Quera-Salva et al. (2010) demonstrated that AGO ameliorated all aspects of sleep-wake abnormalities in patients with depression (particularly falling sleep and the quality of sleep) with an improvement in daytime alertness. The effects of AGO on sleep architecture in MDD have been measured using polysomnography: significant improvements in sleep efficiency, slow-wave sleep, and the distribution of delta activity throughout the night have been documented, but with no change in the amount or latency of rapid eye movement (REM) sleep. Moreover, after AGO treatment, the depressive symptoms of patients suffering from depression were reduced significantly and, on average, the timing of DLMO shifted 3.6-hour earlier, sleep onset was phase-shifted 28-minute earlier, and total sleep time increased by 24 minutes (Robillard et al., 2018).

In adults with autism spectrum disorder with intellectual disability, AGO treatment alleviated circadian-rhythm sleep-wake abnormalities, corrected rhythm disorders of the M5 sleep phase, and had good tolerability (Ballester et al., 2019). O'Neill et al. (2014) revealed AGO administration to result in an immediate and sustained improvement in sleep and the indices of challenging behavior in a man with severe brain damage suffering from a non-24-hour sleep-wake disorder. Armstrong et al. (1993) demonstrated that AGO advanced sleep onset in rats with delayed sleep-phase syndrome, which lays the foundation for further studies of AGO on circadian-rhythm disorders and sleep disorders. Descamps and colleagues showed that AGO could attenuate impairments of sleep-wake architecture, reverse the beta-1 electroencephalogram power band, and improve stress-related rebound of REM sleep in older rats (Descamps et al., 2014). Furthermore, Tchekalova et al. (2020) demonstrated that AGO could adjust circadian homeostasis of motor activity and the sleep-wake cycle in a rat model of chronic constant light, including enhancing the latency of RME sleep and non-REM sleep and upregulating expression of MT₁ and BDNF protein. The researchers previously demonstrated AGO to be effective in restoring impaired circadian patterns and plasma melatonin levels as well as improving depression and anxiety-like behavior in rats exposed to chronic constant light (Tchekalova et al., 2018).

In mammals, melatonin is a neuroendocrine hormone. It is synthesized and secreted principally by the pineal gland at night (Lerner et al., 1960). Its primary physiological function is to convey information concerning the daily cycle of light and darkness to body structures, to regulate circadian rhythms, and to synchronize rhythms. Usually, the rhythmic secretion of melatonin is driven by the circadian clock in the suprachiasmatic nucleus of the hypothalamus. However, light can suppress or synchronize melatonin production according to the light schedule, suggesting that melatonin secretion from the pineal gland is closely related to the duration of darkness (Kennaway, 2019). Melatonin acts via melatonin receptors distributed widely in various tissues to respond to periodic changes of light, such as the sleep-wake cycle. Exposure to light activates the suprachiasmatic nucleus and suppresses melatonin production, which then transmits the light information from the circadian clock and induces awakening in daytime. At night, the synthesis and secretion of melatonin remain high, which promotes sleep (Zisapel, 2018). Therefore, if the rhythmic secretion of melatonin is disrupted, then circadian rhythms are also disrupted (e.g., poor sleep quality and circadian-rhythm sleep-wake disorders). 5-HT and its receptors have been reported to be involved in sleep and wakefulness, as well as cognition and mood. Antagonism of 5-HT_{2A/2C} receptors prolongs the duration of slow-wave sleep and enhances low-frequency (< 7 Hz) activity in the sleep electroencephalogram (Landolt and Wehrle, 2009). Moreover, antagonism of 5-HT_{2C} receptors stimulates dopaminergic and adrenergic pathways and exerts antidepressant and anxiolytic actions in behavioral paradigms, which favors sleep (Millan, 2005). AGO activates MT₁/MT₂ and antagonizes 5-HT_{2C} receptors synchronously, so it has a unique role in regulating the sleep-wake cycle and correcting sleep structure.

Agomelatine and Impairment of Cognition and Memory

A series of studies demonstrated that emotional disorders and sleep disorders can impact the function of memory and cognition negatively (McHutchison et al., 2020; Xu et al., 2020). Neurodegenerative diseases characterized by memory and cognitive impairments (e.g., Alzheimer's disease and dementia) are characterized by abnormal emotional performance and sleep performance. About 50 million people worldwide have dementia (mainly

Alzheimer's disease), and the number is expected to increase to 152 million by 2050 (Alzheimer's Disease International and Patterson, 2018). The estimated total global societal cost of dementia is \$1.3 trillion, which is expected to surpass \$2.8 trillion by 2030 as the number of people living with dementia and care costs increase (World Health Organization, 2021). However, efficacious disease-modifying therapeutics for dementia management are lacking. Interestingly, AGO has been reported to be efficacious in the treatment of emotional disorders, and also in improving cognitive deficits (Bogolepova et al., 2011; Altinyazar and Kiyiluglu, 2016; Callegari et al., 2016).

Additional Table 1 summarizes the effects of AGO on memory impairment and cognitive impairment in clinical trials. Most AGO studies have focused on the treatment of patients with emotional disorders, but some studies have also shown that AGO improves cognitive function in patients with Alzheimer's disease (Altinyazar and Kiyiluglu, 2016), frontotemporal dementia (Callegari et al., 2016), stroke (Bogolepova et al., 2011; Antonen et al., 2015), schizophrenia, or severe depression. Through evaluation of cognitive ability, Englisch et al. (2018) and Bruno et al. (2014) found that AGO treatment could efficiently ameliorate the reasoning/problem-solving ability and correct "perseverative errors" in the Wisconsin Card Sorting Test in patients with schizophrenia (**Additional Table 1**). Moreover, studies have indicated that patients suffering from depression with cognitive impairments (especially those with major depression) had different degrees of improvements in cognitive ability after AGO treatment (Gavrilova et al., 2014; Gorwood et al., 2014, 2015; Kalyn et al., 2015; Cléry-Melin and Gorwood, 2017; Medvedev et al., 2018).

Safarova et al. (2018) and Gavrilova et al. (2015) showed that a combination of AGO and carnitine or AGO and actovegin allowed for a more rapid and pronounced therapeutic effect for cognitive dysfunction in older patients with mild or moderate depression. In a trial involving 20 older patients with mild or moderate depression, AGO reduced anxiety disorder and depressive symptoms effectively as well as improving the health-related quality of life of patients significantly, with a slight increase in the Mini-Mental State Examination score and without pronounced or serious adverse events (Gavrilova et al., 2014). In another trial of 15 patients with primary fibromyalgia, treatment with AGO improved depression, anxiety disorder, and pain significantly in patients; the authors reported a trend towards the improvement of performances in executive/cognitive symptoms (Bruno et al., 2013). Through a double-blind parallel-group design in healthy volunteers, Harmer et al. (2011) observed that AGO (25 mg) decreased the subjective rating of sadness, reduced recognition of sad facial expressions, improved affective memory, and reduced the emotion-potentiated startle response, whereas AGO (50 mg) reduced only the emotion-potentiated startle response without affecting other types of emotional processing. The researchers indicated that AGO is also beneficial for memory improvement in healthy cohorts. Nevertheless, how AGO improves the cognitive dysfunction accompanied by these diseases is not known.

Additional Table 2 summarizes the characteristics of AGO on memory and cognition in healthy animals and pathological animal models. Chronic AGO treatment reduced the error percentage of streptozotocin-treated rats in the eight-arm radial arm maze test, thereby suggesting that AGO could improve the spatial working memory of rats with Alzheimer's disease (Bergamini et al., 2016; Ilieva et al., 2019). Furthermore, Gupta et al. (2015) demonstrated that AGO treatment reduced the escape latency and residence time in the target quadrant in the Morris water maze test of mice with chronic cerebral hypoperfusion, thereby implying that the long-term learning and memory of mice were improved. Moreover, the cognitive function of rats with renovascular hypertension-induced vascular dementia was ameliorated obviously by AGO treatment (Singh et al., 2015). It has also been demonstrated that AGO significantly attenuates 3-nitropropionic acid-induced learning-memory deficits in rats with Huntington's disease (Gupta and Sharma, 2014), and improves the restraint stress-induced impairments of short-term recognition memory and long-term spatial learning and memory in mice and rats (Conboy et al., 2009; Gumuslu et al., 2014; Lapmanee et al., 2017).

Marrocco et al. (2014) found that AGO treatment markedly corrected abnormalities in social-memory performance in adult rats with unstressed or prenatal restraint stress, and Martin et al. (2017) simultaneously observed that effectively alleviated episodic memory deficits of mice with chronic social defeat stress in the novel object recognition test (NORT). Hence, AGO might improve the interactive behaviors of animals by enhancing their recognition memory. In addition, it has been demonstrated that AGO improves the memory deficit induced by scopolamine in mice (Ilkaya et al., 2015), and alleviates the short-term memory despair of mice injected with pentylenetetrazol to induce kindling (Azim et al., 2017), but did not correct spatial-memory impairment in rats suffering from epilepsy induced by kainate acid (Tchekalova et al., 2017). Those findings suggest that the effects of AGO treatment in various animal models differ because of different epilepsy-triggering treatments, which provides a direction for study on the pharmacological mechanism of AGO. In the probabilistic reversal-learning test, Drozd et al. (2019) found that AGO treatment improved the ability of cognitive judgment in pessimistic rats. Notably, single administration of AGO (10 and 40 mg/kg) in the evening or morning improved the recognition memory of normal rats significantly in the NORT (Bertaina-Anglade et al., 2011). Moreover, studies in normal rats revealed that long-term AGO treatment enhanced spatial memory obviously in the Morris water maze test (Demir Özkay et al., 2015), and improved recognition memory in the NORT (Ladurelle et al., 2012). How AGO improves memory and cognitive function is

not known, probably owing to the perplexing causes of memory impairment and cognitive impairment in particular diseases.

It has been demonstrated that AGO reduced amyloid β -42 ($A\beta_{42}$) accumulation in the frontal cortex and hippocampus of male rats with streptozotocin-induced Alzheimer's disease (Ilieva et al., 2019), activated melatonin receptors, and prevented $A\beta$ -induced tau phosphorylation by activation of GSK3 β and oxidative damage in PC12 cells (Yao et al., 2019). Furthermore, chronic administration of AGO completely prevented the stress-induced increase in glutamate release in the prefrontal/frontal cortex of rats by the synergistic effect of melatonergic and 5-HT $_{2C}$ receptors in one study (Tardito et al., 2010). Recently, Ilieva et al. (2021) suggested that chronic treatment with AGO alleviated anxiety disorder and depressive-like behavior and decreased the $A\beta$ level in the hippocampus by enhancing α -secretase and decreasing γ -secretase in a rat model of Alzheimer's disease. Cankara et al. (2021) showed that AGO attenuated cisplatin-induced neurotoxicity in a mouse hippocampal neuronal cell line (HT22), and improved cisplatin-induced deficits in memory and recognition. In addition, in rat models with cognitive impairments, AGO also reversed neuronal loss in the hippocampus (Can Ö et al., 2018; Ilieva et al., 2021) and caused significant enhancement in the volume of hippocampal CA1–3 subfields and the total number of pyramidal neurons in this region (Demir Özkay et al., 2015), thereby implying that AGO had neuroprotective effects.

BDNF is a neurotrophin distributed widely in the mammalian brain. BDNF has prominent functions in plastic regulation, including control of neuronal and glial development, neuroprotection, and modulation of short- and long-lasting synaptic interactions, which are critical for cognition and memory (von Bohlen Und Halbach and von Bohlen Und Halbach, 2018). It has been reported that AGO alleviates depressive symptoms effectively in patients suffering from depression, with restoration of the plasma level of BDNF (Martinotti et al., 2016). AGO also increases the hippocampal BDNF level and the number of BDNF-positive neurons in rats with chronic unpredictable mild stress (Lu et al., 2018). Notably, Ladurelle et al. (2012) demonstrated that chronic administration of AGO increased the level of mature BDNF in the hippocampus significantly, and promoted rapid, sustained, enhanced cognitive activity in normal rats.

Cyclic adenosine monophosphate-responsive element binding protein (CREB) is a transcription factor. CREB regulates expression of several genes involved in the control of neuroplasticity, circadian rhythms, cell survival, and cognition (Carlezon et al., 2005). Moreover, CREB is a pivotal component of the "molecular switch" that converts short-term memory to long-term memory (Lisman et al., 2018). Furthermore, the CREB family is a major regulator of BDNF expression after tropomyosin receptor kinase B (TrkB; a BDNF receptor) signaling (Esvold et al., 2020). Recent evidence suggests that chronic administration of AGO leads to improvements in memory deterioration and upregulation of hippocampal expression of CREB and BDNF in mice exposed to unpredictable, chronic, mild stress (Gumuslu et al., 2014). It has been revealed that activation of MT $_1$ and MT $_2$ activates ERK-90 kDa ribosomal S6 kinase-CREB-BDNF signaling (Sung et al., 2018) and BDNF-TrkB signaling in hippocampal neurons (Li et al., 2018). Moreover, mice with deletion of the 5-HT $_{2C}$ receptor show increased levels of the mature form of BDNF in the hippocampus (Hill et al., 2011). In naïve rats, Musazzi et al. (2014) found that chronic administration of AGO—contrary to traditional antidepressants—did not increase CREB phosphorylation, but instead modulated the mitogen-activated protein kinase (MAPK)-ERK1/2 and AKT-GSK3 β pathways. ERK1/2 is one of the best-characterized members of the MAPK family. ERK1/2 mediates the proliferation, differentiation, apoptosis, inflammation, and synaptogenesis of cells (Albert-Gascó et al., 2020).

In neurons, an important function of ERK-MAPK signaling is regulation of synaptic plasticity, which relates to learning and memory processes (Alkadhhi and Dao, 2019). Several studies have indicated that phosphatidylinositol 3-kinase can activate AKT in brain cells and, by activation of this protein, GSK3 β , which inhibits tau hyperphosphorylation (Chen et al., 2004; Endo et al., 2006). AKT shows high expression in some brain areas that are known to regulate cognition and neuroprotection, thereby having a key role in synaptic and neural survival, neuroprotection, and neural plasticity, as well as supporting the growth and survival of neurons (Beaulieu et al., 2009; Kitagishi et al., 2012). Studies have reported that activation of melatonin receptors (MT $_1$ and MT $_2$) can activate MAPK-ERK1/2 and AKT-GSK3 β signaling pathways (Werry et al., 2005; Hadj Ayed Tka et al., 2015; Chagraoui et al., 2016; Li et al., 2020). Therefore, AGO may protect hippocampal neurons and improve memory and cognition by regulation of MAPK-ERK and AKT-GSK3 β signaling pathways, but this concept has not been demonstrated definitively.

It has been shown that 5-HT $_{2C}$ receptors mediate Ca $^{2+}$ release from endoplasmic reticulum via the phospholipase C-inositol 1,4,5-trisphosphate-Ca $^{2+}$ pathway (Watson et al., 1995; Wada et al., 2006). 5-HT $_{2C}$ receptors show high expression and are upregulated in the brains of mice with acute infusion of $A\beta$ (Bonn et al., 2013) and in rats with pilocarpine-induced epilepsy with memory impairment (Krishnakumar et al., 2009). Those studies indicate that intracellular Ca $^{2+}$ dysregulation might (at least in part) result from 5-HT $_{2C}$ overexpression. Ca $^{2+}$ dysregulation leads to neuronal apoptosis and cell death, which result in memory impairment and cognitive impairment (Kumar, 2020). Scholars have applied various sequencing methods and databases and analyzed "omics" data to discover new uses for existing drugs. Such studies have demonstrated AGO to also be involved in regulation of axon development, glutamatergic activity, netrin signaling, synaptic long-term potentiation, and Rho-GTPases-related pathways (an important regulator of

morphological neuroplasticity) in hippocampal neurons (Patrício et al., 2015), as well as a neurotrophin signaling pathway and insulin signaling pathway in patients suffering from depression (Dmitrzak-Weglaz et al., 2021), which are closely related to memory and cognitive function.

Although the findings mentioned above are not entirely consistent (possibly caused by different animal models and interventions), they show that AGO improves memory and cognitive function by activating multiple signal-transduction pathways (Figure 1). Clinical and basic-science studies investigating the effect of AGO on memory and cognition suggest that AGO might be a novel strategy for the treatment of memory impairment and cognitive impairment. With the increase in age of populations worldwide, the dementia observed in degenerative diseases has become a growing public-health problem. However, prevention of the memory impairment and cognitive impairment of patients with dementia is not possible, and few drugs can be used for treatment. With its unique pharmacological effects, AGO provides a new idea for the treatment of dementia.

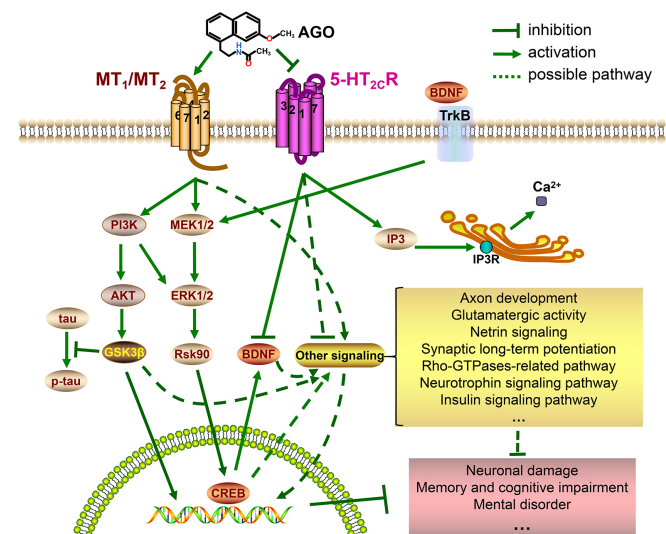


Figure 1 | Pathways involving the neuroprotective effects of AGO (schematic).

Through MT $_1$ /MT $_2$, AGO can activate PI3K-AKT-GSK3 β and MAPK-ERK1/2-RSK90-CREB cascades, which control gene transcription or protein modification. Activation of GSK3 β inhibits tau phosphorylation. CREB can control BDNF transcription. By inhibiting the 5-HT $_{2C}$ receptor (5-HT $_{2C}$ R), AGO can also inhibit IP3 from releasing Ca $^{2+}$ from the endoplasmic reticulum, and promote expression of BDNF which combined with TrkB and activate the MAPK-ERK1/2-RSK90-CREB signaling pathway. 5-HT $_{2C}$: 5-Hydroxytryptamine 2C; AGO: agomelatine; AKT: protein kinase B; BDNF: brain-derived neurotrophic factor; CREB: cyclic adenosine monophosphate-response element binding protein; ERK: extracellular signal-related kinase; GSK3 β : glycogen synthase kinase 3 β ; IP3: inositol 1,4,5-trisphosphate; MAPK: mitogen-activated protein kinases; MT $_1$: melatonin receptor 1A; MT $_2$: melatonin receptor 1B; PI3K: phosphatidylinositol-3-kinase; RSK90: 90 kDa ribosomal s6 kinase; TrkB: tropomyosin-related kinase B.

Limitations of Agomelatine

Although AGO possesses some distinct advantages, it also has some disadvantages. The commonly reported adverse events in clinical treatment using AGO are headache, nausea and fatigue, which are of mild-to-moderate severity (Stein et al., 2018). Moreover, due to its propensity to increase the level of liver enzymes, AGO is contraindicated in patients with impaired liver function (Štuhec, 2013; Friedrich et al., 2016). Hence, monitoring of liver function is recommended before AGO initiation and periodically during treatment. Nevertheless, developing AGO analogs with low toxicity and few side effects for the treatment of chronic neurodegenerative diseases is important.

Conclusions

The most remarkable feature of AGO is a synergistic action between its agonism at MT $_1$ /MT $_2$ and antagonism at 5-HT $_{2C}$ receptors. Given its innovative mechanism of action and favorable safety profile, AGO is beneficial for the treatment of mood disorders and sleep disorders, and most reviews have focused on these aspects. Unlike those reviews, in light of the neuroprotective effects of AGO, we have summarized research progress regarding the improvement of memory and cognitive function using AGO. However, the few studies undertaken so far on the clinical treatment of cognition and dementia by AGO (particularly on the specific treatment of neurodegenerative diseases) need to be bolstered with additional studies. Nevertheless, clinical studies and animal experiments have strongly suggested that AGO could be a promising treatment option for improving memory, sleep, and mental activity simultaneously.

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Additional files:

Additional Table 1: Characteristics of AGO for the treatment of memory and cognitive impairments in clinical studies.

Additional Table 2: Characteristics of AGO for the treatment of memory and cognitive impairments in animal studies.

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Additional Table 1 Characteristics of AGO for the treatment of memory impairment and cognitive impairment in clinical studies

Study design	Patients	Agent and dose (route)	Primary measure and results	Conclusions	Study
1 month, case report	1 AD patient	AGO (25 mg/d, p.o.)	MMSE; MMSE score: 19 (before AGO treatment) vs. 23 (after 1-month AGO treatment)	Significant improvement in cognitive function	Altınyazar and Kiylioglu, 2016
10 wk, double-blind	24 FTD patients	AGO (50 mg/d, p.o.) or melatonin (10 mg/d, p.o.)	AES-C; 50.6 ± 2.4 (AGO) vs. 42.7 ± 2.4 (melatonin), $P = 0.006$	Significant reduction of apathy and improvement in cognitive function by AGO, but not melatonin	Callegari et al., 2016
6–8 wk, randomized	2048 MDD patients	AGO (25 or 50 mg/d, p.o.)	TMT-A, TMT-B, d2 test; 67.68% of patients were responders and 43.31% were in remission	Significant improvement in cognitive function	Gorwood et al., 2014
8 wk, single-blind	42 patients with mild-to-moderate depression	Antidepressant monotherapy (fluvoxamine, venlafaxine or AGO, 25 mg/d) or use the same antidepressant in combination with actovegin (p.o.)	MMSE; 26.23 ± 2.32 (day 0) vs. 28.44 ± 1.49 (day 56), $P < 0.01$ 10-word memory test; 6.42 ± 0.97 (day 0) vs. 7.00 ± 0.89 (day 56), $P < 0.01$ Drawing of clock; 8.04 ± 1.24 (day 0) vs. 8.81 ± 1.08 (day 56), $P < 0.01$	Significant improvement in cognitive function, with faster improvement in cognitive function by the antidepressant in combination with actovegin	Safarova et al., 2018
7 d, double-blind	48 healthy volunteers	AGO (25–50 mg/d, p.o.)	Facial expression recognition task; AGO (25 mg) vs. placebo (group × emotion $F(6, 174) = 2.6$, $P = 0.018$), AGO (50 mg) vs. placebo (group × emotion $F(6, 180) = 0.8$, $P = 0.6$)	Significantly reduced subjective ratings of sadness, reduced recognition of sad facial expressions, improved positive affective memory and reduced emotion-potentiated startle response with 25 mg of AGO, but not 50 mg of AGO	Harmer et al., 2011
12 wk, proof-of-concept study	27 patients with schizophrenia and comorbid depression	Antipsychotic drugs in combination with AGO (p.o.)	MCCB; composite score (baseline vs. after treatment, $P = 0.01$), reasoning/problem-solving subscore (baseline vs. after treatment, $P = 0.001$)	Significant improvement in the MCCB composite score and the reasoning/problem-solving subscore	Englisch et al., 2018

2–8 wk, randomized study	33 patients with CBI and comorbid mild depression	AGO (25 mg/d, p.o.)	MMSE, MoCA; baseline vs. after treatment, $P < 0.001$	Significant improvement in cognitive function	Antonen et al., 2015
6 wk, randomized study	35 patients with depression and marked cognitive impairment	AGO (25 mg/d, p.o.)	MMSE, Rey test for auditory-speech learning, RAVLT; 74.3% of patients were responders and 51.4% were in remission	Significant improvement in cognitive function	Medvedev et al., 2018
16 wk, open-label uncontrolled trial	20 patients with schizophrenia	AGO (50 mg/d, p.o.)	Wisconsin Card Sorting Test; perseverative errors: 14.75 ± 10.05 (baseline) vs. 11.25 ± 10.46 (week 16), $P = 0.033$, Cohen's $d = 0.3$	Significant improvement in performances of the Stroop task and “perseverative errors” in the Wisconsin Card Sorting Test	Bruno et al., 2014
12 wk, open-label, preliminary study	15 FMS patients	AGO (25 mg/d, p.o.)	Wisconsin Card Sorting Test; perseverative errors: 26.87 ± 30.963 (baseline) vs. 25.13 ± 30.223 (week 16), $P = 0.301$, Cohen's $d = 0.1$	Improvement in cognitive function	Bruno et al., 2013
6–8 wk, multicenter study	2048 outpatients with depression	AGO (25 mg/d, p.o.)	TMT-A, TMT-B, d2 test; TMT-A (time) and TMT-B (time): $P < 0.0001$, TMT-A (mistakes): $P = 0.0004$, TMT-B (mistakes): $P < 0.0001$, F1 (number of omission mistakes): $P < 0.05$	Significant improvement in d2, TMT-A, and TMT-B tests	Cléry-Melin and Gorwood, 2017
42 d, randomized study	18 patients with depression	AGO (25–50 mg/d, p.o.)	MMSE; 26.76 ± 3.30 (day 0) vs. 28.17 ± 2.0 (day 42)	Improvement in cognitive function	Kalyn et al., 2015
6 wk, multicenter, observational, phase-IV study	1565 patients with depression	AGO (25–50 mg/d, p.o.)	MATHyS; 4.05 ± 1.11 (baseline) vs. 4.87 ± 1.16 (week 6), $P < 0.001$	Significant improvement in cognitive function	Gorwood et al., 2015
8 wk, randomized study	40 patients with mild-to-moderate depression	Antidepressant monotherapy (fluvoxamine, venlafaxine)	MMSE; 26.90 ± 2.10 (day 0) vs. 28.15 ± 1.53 (day 56), $P < 0.05$;	Significant improvement in cognitive function, but faster improvement using the antidepressant in combination with carnitine	Gavrilova et al., 2015

		or AGO, 25–50 mg/d) or use the same antidepressant in combination with carnitine (p.o.)	10-word memory test; 6.68 ± 0.86 (day 0) vs. 6.92 ± 0.96 (day 56)		
			Drawing of clock; 7.92 ± 1.18 (day 0) vs. 8.33 ± 1.23 (day 56)		
3 months, randomized study	40 patients with post-stroke depression	AGO (25 mg/d, p.o.)	MMSE; 25.2 ± 1.1 (0 day) vs. 27.2 ± 0.6 (month 3)	Improvement in cognitive function	Bogolepova et al., 2011
6 wk, randomized study	20 older patients with mild-to-moderate depression	AGO (25–50 mg/d, p.o.)	MMSE; median MMSE score before treatment = 28.5 and at study termination = 29.5 ($P >$ 0.05)	AGO had no effect on cognitive function and did not elicit pronounced or serious adverse events, but the cognition of patients showed an increase	Gavrilova et al., 2014

AD: Alzheimer's disease; AES-C: apathy evaluation scale-clinician version; AGO: agomelatine; CBI: chronic brain ischemia; FMS: fibromyalgia syndrome; FTD: frontotemporal dementia; MATHyS: multidimensional assessment of thymic states; MCCB: measurement and treatment research to improve cognition in schizophrenia consensus cognitive battery; MDD: major depressive disorder; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; p.o.: per os; RAVLT: Rey auditory verbal learning test; TMT-A: trail-making test-A; TMT-B: trail-making test-B.

Additional Table 2 Characteristics of AGO for the treatment of memory impairment and cognitive impairment in animal studies

Study model	Animal	Agent and dose (route)	Main results and conclusion	Study
CCH	Mouse	AGO (2–4 mg/kg per day, i.p.), 24 d	In the Morris water maze test, AGO treatment decreased escape latency time in CCH-induced mice ($P < 0.05$). AGO improved long-term memory.	Gupta et al., 2015
Renovascular hypertension induced-vascular dementia	Rat	AGO (2–4 mg/kg per day, i.p.), 24 d	In the Morris water maze test, the escape latency time was reduced significantly on day 4 (40.1 ± 2.6 (2-mg AGO) and 39.8 ± 2.59 (4-mg AGO), $P < 0.001$). AGO improved long-term memory.	Singh et al., 2015
3-Nitropropionic acid-induced Huntington's disease	Rat	AGO (2–4 mg/kg per day, p.o.), 28 d	In the Morris water maze test, AGO treatment reduced the escape latency time significantly on day 4 ($P < 0.001$) as compared with that in the 3-3-nitropropionic acid-treated group. AGO improved long-term memory.	Gupta and Sharma, 2014
Streptozotocin-induced model of AD	Rat	AGO (40 mg/kg per day, i.p.), 30 d	In the radial arm maze test, AGO treatment decreased working memory error ($P < 0.01$). AGO improved working memory.	Ilieva et al., 2019
PRS	Rat	AGO (40 mg/kg per day, i.p.), 21 d	In the social memory test, PRS rats treated with AGO displayed a reduction in sniffing behavior compared with vehicle-treated PRS rats ($P < 0.05$). AGO improved social memory performance.	Marrocco et al., 2014
Restraint-induced stress	Rat	AGO (10 mg/kg per day, i.p.), 4 wk	In the Morris water maze test, AGO-treated stressed rats exhibited a reduction in escape latency on days 1 ($P < 0.01$), 2 ($P < 0.001$), and 3 ($P < 0.001$) and correct quadrant time ($P < 0.001$) compared with vehicle-treated stressed rats. AGO improved long-term memory. In the novel object recognition test, a higher discrimination ratio was evidenced in AGO-treated rats than in vehicle-treated stressed rats ($P < 0.05$). AGO improved recognition memory.	Lapmanee et al., 2017
Chronic social defeat stress	Mouse	AGO (10 mg/kg per day, i.p.), 3 wk	In the novel object recognition test, stressed-AGO mice displayed a significantly increase in the recognition index compared with stressed (hydroxyethylcellulose-treated) mice ($P < 0.05$). AGO improved recognition memory.	Martin et al., 2017
Memory deficit induced by scopolamine	Mouse	AGO (1, 10, or 30 mg/kg per day, i.p.), 30 min before testing	In the passive avoidance task, AGO (30 mg/kg) significantly increased the retention time as compared with scopolamine ($P < 0.05$). AGO alleviated episodic memory deficit.	İlkaya et al., 2015
Pentylenetetrazol-induced kindling	Mouse	AGO (10 mg/kg per day, p.o.), 3 wk	In the Y maze test, AGO treatment significantly enhanced percentage alternation and the number of arm entries ($P < 0.001$) following PTZ	Azim et al., 2017

Chronic mild stress-induced cognitive deterioration	Mouse	AGO (10 mg/kg per day, i.p.), 5 wk	kindling-induced seizures. AGO improved working memory. In the Morris water maze test, AGO shortened the escape latency significantly in the familiarization session ($P < 0.001$) and increased the time spent in the escape platform quadrant ($P < 0.01$). AGO improved long-term memory. In the novel object recognition test, AGO increased the ratio index significantly compared with stress-exposed control mice ($P < 0.001$).	Gumuslu et al., 2014
Normal	Rat	Single intraperitoneal administration of AGO (10–40 mg/kg) in the evening or AGO (2.5, 10, or 40 mg/kg) in the morning	AGO improved recognition memory In the novel object recognition test, AGO (10 and 40 mg/kg) increased the recognition index significantly ($P < 0.01$). AGO improved recognition memory in the morning or evening.	Bertaina-Anglade et al., 2011
Stress	Rat	AGO (10 mg/kg per day, i.p.), 22 d	In the radial-arm water maze test, AGO treatment reduced arm-entry errors significantly in non-stressed and stressed rats ($P < 0.001$). AGO blocked the predator stress-induced impairment of spatial memory and improved spatial memory.	Conboy et al., 2009
Normal	Rat	AGO (40 mg/kg per day, i.p.), 20 wk	In the Morris water maze test, AGO-treated rats located the hidden platform significantly faster than did control rats on days 2 ($P < 0.01$), 3 ($P < 0.001$), and 4 ($P < 0.01$). During the probe trial, AGO-treated rats spent significantly more time ($P < 0.001$) in the target quadrant compared with that of control rats. AGO enhanced spatial memory.	Demir Özkay et al., 2015
Normal	Rat	AGO (40 mg/kg per day, i.p.), 22 d	In the novel object recognition test, AGO increased the D2 index (ability to discriminate between a familiar object and novel object) ($P < 0.05$). AGO improved recognition memory.	Ladurelle et al., 2012
KA status epilepticus	Rat	AGO (40 mg/kg per day, i.p.), 10 wk	In the radial arm maze test, KA-vehicle and KA-AGO groups exhibited more working memory errors compared with naive rats treated with vehicle after the	Tchekalarova et al., 2017

Streptozotocin-induced model of type-2 diabetes mellitus	Rat	AGO (40–80 mg/kg per day, i.p.), 2 wk	first session ($P < 0.05$). AGO had no effect on kainate acid-induced memory impairment. In the Morris water maze test, diabetic rats treated with AGO (40 mg/kg) exhibited a significant reduction of escape latency on day 4 ($P < 0.001$). Administration of AGO at 40 ($P < 0.05$) or 80 mg/kg ($P < 0.01$) induced a significant increase in the target quadrant time of diabetic rats. AGO treatment reversed the impaired long-term learning and memory performance of diabetic rats effectively. In the passive avoidance task, treating diabetic rats with 40 ($P < 0.05$) or 80 mg/kg ($P < 0.001$) of AGO prolonged the entrance latency to the dark compartment. AGO improved episodic memory deficit.	Can Ö et al., 2018
Chronic psychosocial stress	Mouse	AGO (10–25 mg/kg per day, p.o.), acute treatment or 12 d	Although there was no stress $\times$ drug interaction or main effect of drug in the simple reversal learning test, mice completed more reversals after AGO (25 mg/kg) ($P < 0.05$) treatment relative to vehicle-treated naive mice in the complex reversal learning test. AGO reversed cognitive deficits partially.	Bergamini et al., 2016
“Pessimistic” and “optimistic” traits	Rat	AGO (5, 10, or 40 mg/kg per day, p.o.), acute treatment	Following acute treatment with AGO, the proportion of lose-shift behavior in the probabilistic reversal-learning test was reduced significantly in pessimistic rats compared with optimistic rats ($P < 0.05$).	Drozd et al., 2019
Intracerebroventricular $A\beta_{1-42}$ model of AD	Rat	AGO (40 mg/kg per day, i.p.), 30 d	AGO treatment did not improve spatial memory of the $A\beta$ group in the radial arm maze test, but AGO enhanced the α-secretase concentration ($P < 0.05$) and decreased the γ-secretase concentration ($P < 0.05$ or $P < 0.01$) in the hippocampus, with decreased $A\beta_{1-42}$ levels in the frontal cortex and hippocampus ($P < 0.01$ or $P < 0.001$).	Ilieva et al., 2021
Cisplatin-induced model	Rat	AGO (20–40 mg/kg, p.o.), 7 d	In the passive avoidance test, AGO (20 and 40 mg/kg) improved the cisplatin-induced decrease in the step-through latency significantly ($P < 0.001$). In the novel object recognition test, AGO (20 and 40 mg/kg) attenuated the cisplatin-induced decrease in the discrimination index significantly ($P < 0.05$). AGO improved memory retention and recognition.	Cankara et al., 2021

AD: Alzheimer’s disease; AGO: agomelatine; $A\beta$: amyloid β ; CCH: chronic cerebral hypoperfusion; i.p.: intraperitoneal; KA: kainate acid; p.o.: per os; PRS: prenatal restraint stress.