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Review Article

Galantamine: A Review Update

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Abstract

Galantamine, like nor-belladine, is a benzazepine. Galanthus and other plants of the Amaryllidaceae are the most common sources of it. Galantamine is used to combat the muscle effects of gallamine triethiodide and tubocurarine by acting as a cholinesterase inhibitor. The review reveals the protective effects of galantamine on the functions and integrity of the liver, brain and memory impairment. Various independent studies have shown anti-Alzheimer, antioxidant, antidiabetic and neuroprotective effect of galantamine. The current review highlights current knowledge and the health-promoting effects of a drug known as galantamine. This review summarizes the current state in the pharmacology of galantamine, focusing on its effects on tolerance, dosage, drug interactions and pharmacological studies in animal models.

Keywords: Galantamine, Pharmacology, Acetylcholinesterase inhibitor, Neuroprotective, Protective effect.

Introduction

Galantamine, like nor-belladine, is a benzazepine. Galanthus and other Amaryllidaceae plants are the most common sources of it. Galantamine is used to counteract the muscle effects of gallamine triethiodide and tubocurarine by acting as a cholinesterase inhibitor. It's been studied for Alzheimer's disease and other central nervous system disorders in various ways. The bioactive molecule galantamine was unintentionally found in the early 1950s, and plant extracts were first employed to treat nerve pain and poliomyelitis, according to the pharmacological history of galantamine [1]. In the early 1950s, galantamine was developed as a clinically useful medication. According to sources, a Russian pharmacologist discovered that local peasants living at the foot of the Ural Mountain utilised wild Caucasian snowdrop to cure poliomyelitis in children [2]. Galantamine's AChE inhibitory capabilities and antagonising effects on curare activity were discovered in a research published in 1951 [1]. Galantamine was initially discovered in 1952 from the perennial herbaceous plant Galanthus woronowii of the Amaryllidaceae family [3]. Several preclinical researches on Galantamine's pharmacology were conducted in the late 1950s. Galantamine's antagonistic effects against non-depolarizing neuromuscular blocking drugs (proven in pre-clinical research on neuromuscular preparations of cats in situ, in vitro studies on frog rectus abdominis muscle, and so on) were among the findings. In Bulgaria, galantamine was sold under the brand name "NIVALIN." In the early 1960s, an in vivo investigation in an anaesthetized cat yielded the first evidence of Galantamine's anti-cholinesterase effect [4]. Later, preclinical study began, and researchers looking for new Alzheimer's disease therapies began looking at galantamine's therapeutic properties [5–7]. By the 1990s, Galantamine had been licenced as a treatment for Alzheimer's. Galantamine received its initial permission of license in Iceland, Ireland, Sweden, and the United Kingdom for the treatment of Alzheimer's disease in 1996, thanks to Sanochemia Pharmaceutical's first patent on the synthesis method of galantamine [8,9]. Galantamine is now licenced as a first-line treatment for Alzheimer's disease in the United States, several European countries, and a few Asian nations. It is a CNS AChE inhibitor and allosteric potentiating ligand of the neuronal cholinergic nicotinic receptors that has been clinically licenced for the treatment of Alzheimer's disease [10]. Anti-inflammatory [11] and antioxidant [12] properties are also present. It was also reported to be used in antidiabetic medication in 2009 [1,13].

Chemistry

Galantamine's IUPAC designation is (4aS,6R,8aS)-5,6,9,10,11,12-hexahydro-3-methoxy-11-methyl-4aH-[1]benzofuro[3a,3,2-ef]benzofuro[3a,3,2-ef]benzofuro[3a,3,2-ef]benzofuro[3a,3,2-ef]benzofuro[3a,3, [2]benzazepin-6-ol, commonly known as galanthamine, is an alkaloid that is a phenanthrene derivative. It has a molecular structure similar to morphine. Galantamine's empirical formula is C17H21NO3 with a molecular weight of 287.35 g/mol. Galantamine has a melting point of 269–270 degrees Celsius (HBr salt) and a solubility of 10 mg/mL in water (HBr salt). It's soluble in hot water, alcohol, acetone, and chloroform, but less so in benzene and ether. Galantamine yields from the Leucojum aestivum plant range from 0.1 to 2% of dry weight [14,15]. Classification of the galanthamine as given in Table 1;

Table 1: Scientific classification of galanthamine	
Kingdom	Organic compounds
Super class	Alkaloids and derivatives
Class	Amaryllidaceae alkaloids
Sub class	Galanthamine-Type Amaryllidaceae alkaloids
Direct parent	Galanthamine-Type Amaryllidaceae alkaloids

Synthesis of galanthamine: Galanthamine synthesis based on two approaches as follows:

1. **Biomimetic approach: Using phenolic oxidative coupling**

a. **Using norbelladine derivative:** Galantamine may be generated from a common precursor norbelladine by intramolecular oxidative phenol coupling, as discovered by Barton et al. in the 1960s [16]. Using R-14C-labeled norbelladine derivatives as precursor materials, it was hypothesised that norbelladine is the biogenetic precursor for galantamine production [17,18]. After oxidative phenol coupling, a dienone was thought to be the main step that created narwedine, and it was dubbed the precursor to galantamine [15,19].

b. **Using 4-O-methylnorbelladine:** For galantamine production, another strategy utilises oxidative phenol coupling of 4-O-methylnorbelladine to a dienone. Dienone undergoes intramolecular ring closure of the ether bridge, resulting in the formation of N-demethylnarwedine. Galantamine is obtained through stereo selective reduction and N-methylation [15].

2. **The stereo-selective approach: Intramolecular heck reaction**

In 2000, Fels [20] and Parsons [21] described a stereo selective method for synthesizing galantamine based on the intramolecular Heck reaction [22]. From â, γ-unsaturated ester 1 and benzaldehyde 2, Fels created the cyclohexenyl, aryl ether 3. Then, in the presence of potassium carbonate, compound 3 was exposed to a reaction with tetrakis (triphenylphosphine) palladium (0), yielding compound 4 in 66%. Using â, γ-unsaturated amide 5 and benzaldehyde 6, Parsons produced an iodide 7. Iodide 7 was refluxed with $Pd(OAc)_2$ and silver carbonate in DMF to create benzofuran 8 in a 75 percent yield. Both compounds 3 and 8 were transformed to the identical derivative 9 in the end [15].

Pharmacokinetics of galanthamine

The medication has a bioavailability of roughly 90% and pharmacokinetics that are dosage dependant. The distribution volume is high, while protein binding is minimal (28.3-33.8 percent). The cytochrome P450 system, especially the CYP2D6 and CYP3A4 isoenzymes, is involved in metabolism. In urine, it seems to be 20-25 percent unaltered [1,23].

Pharmacodynamics of galanthamine

1. **Effect on Acetylcholine-esterase activity:** Cholinergic (AChE) is a neurotransmitter that is generated in the presynaptic neuron and released into the synaptic cleft where it binds reversibly to distinct types of acetylcholine receptors [24]. These receptors are known as nicotinic and muscarinic. Galantamine acts as a selective and competitive inhibitor of AChE, which is thought to be responsible for ACh hydrolysis at the neuromuscular junction. This junction can be found in peripheral and central cholinergic synapses, as well as in parasympathetic target organs. As galantamine binds to AChE, acetyl choline degradation is slowed, resulting in higher acetylcholine levels in the synaptic cleft. According to X-ray crystallographic data, galantamine binds to the active site of AChE reversibly [15,25]. Because the medication attaches at the base of the active site gorge, it interacts with two binding sites through hydrogen bonding. The choline binding site [amino acid 84 (tryptamine)] and the acyl-binding pocket are two of these sites (amino acids 288 and 290; both phenylalanine) [26].

   Ex vivo investigation on human brain postmortem and fresh cortical biopsy samples revealed that the IC50 values for the frontal cortex and hippocampus areas of the brain were 3.2 and 2.8 mmol/L, respectively [27]. Galantamine was shown to be less effective in inhibiting AChE than tacrine or physostigmine, and it was 10 times less effective at inhibiting brain AChE than erythrocyte AChE [27]. Galantamine has a 53-fold selectivity for AChE [15,28] over butyryl cholinesterase [29].

2. **Effects on nicotinic acetylcholine receptors:** When compared to other similar agonists (acetylcholine, nicotine, and other nicotinic agonists) that share routes with other inotropic neuroreceptors, activation of nAChRs appears to be favorably controlled by a secondary unique mechanism [15]. Galantamine is classified as an allosterically potentiating ligand because it increases the effect of acetylcholine on nAChRs by binding at an allosteric location [30]. Galantamine seems to bind allosterically to the a-subunit of nAChRs at a location distinct from that of ACh, as determined by affinity labelling and immunohistochemistry [15], causing conformational changes in the receptor. The action of galantamine at these receptors was also inhibited by a monoclonal antibody FK1 [31], which is a selective inhibitor of the a- subunit of the receptor [15].

3. **Effects on Animal Models' Behavior and Memory:** [32] assess memory impairment, a surgical mouse model was used. After previous training, mice were placed on working memory and reference activities for 24 hours [33,34]. Galantamine was injected intraperitoneally into it. As a result of galantamine action, mice with impaired memory exhibited improved working memory, as evidenced by a decrease in work duration. Other rat experiments were performed in the same way as before [35]. Galantamine, physostigmine, and tacrine were given in increasing amounts in mice. Mice were asked to sit in a wooden area surrounded by an electrical grid to complete the task of avoiding them. All three of the drugs used increase the amount of time spent avoiding certain actions Galantamine has provided significant improvements in much lower doses and shorter doses compared to physostigmine or tacrine [15].

4. **Effect on brain (Neuroprotective action):** Agonists nAChRs have been shown to protect neuronal cells [36] against glutamate [37], tropic-factor depletion [38], hypoxia [39], and alpha-beta amyloid toxicity [40]. In mice and non-human mice, they improve memory and reading ability. Humans have also become increasingly attentive and digesting information quickly [41]. In their study, Nakamizo et al. (2005) [42] found that nicotine use reduced mortality of glutamate-induced motor neuron in basic rat spinal cord cultures. Dihydro-β-erythroidin (DH β E) or α-bungarotoxin (αBT) was shown to inhibit nicotine-induced neuroprotection. It has recommended the removal of both $\alpha_4\beta_2$ and α_7 nAChRs. In this framework, the hypothesis was developed that galantamine could mediate neuronal protection against several neurotoxic agents by elevating the effects of ACh on nicotinic receptors [15,43].

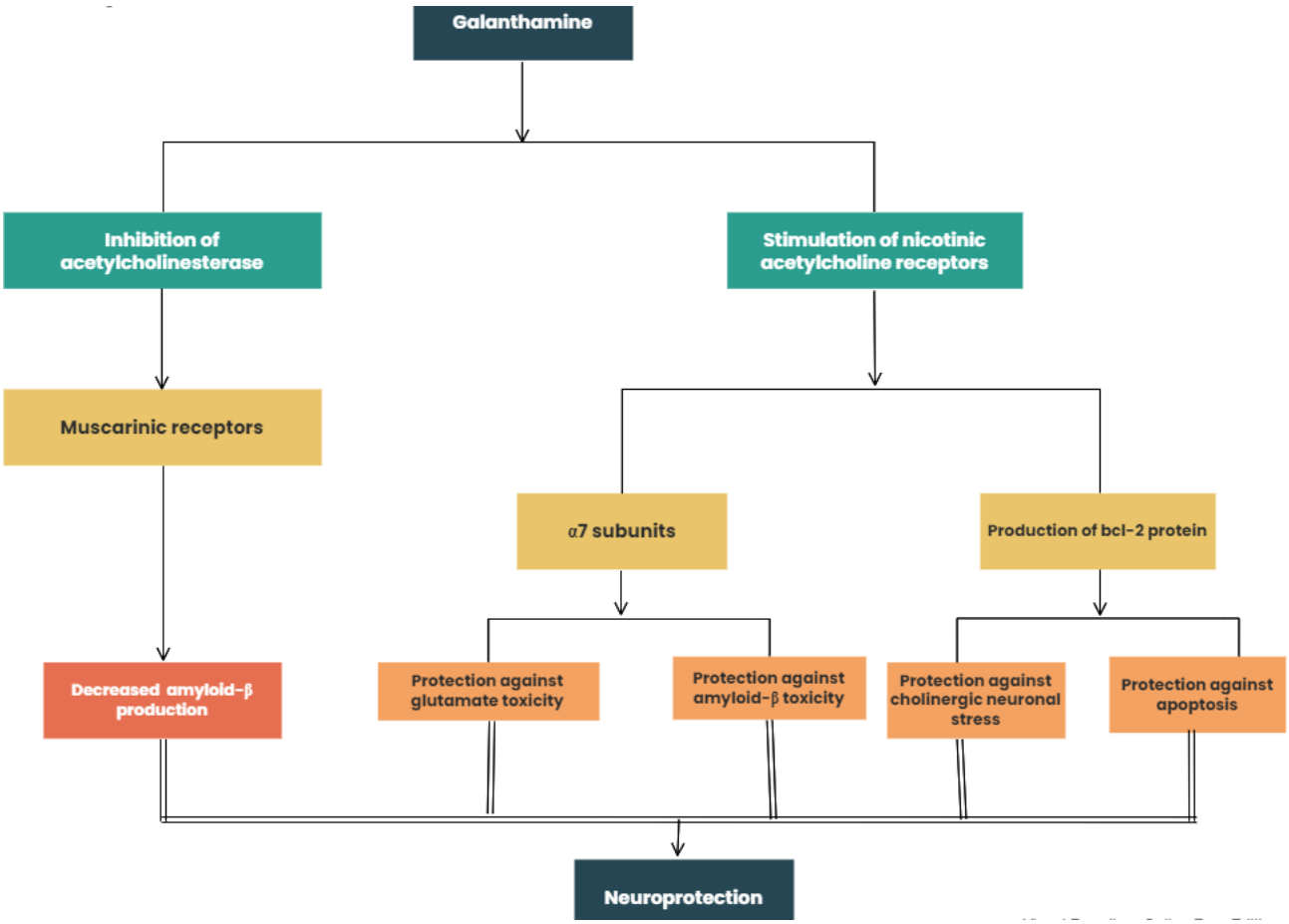

Figure: 1 Neuroprotective action [15]

5. **Inflammation-Reducing Effect (Anti-inflammatory activity):** Altering the anti-inflammatory actions of galantamine has resulted in a reduction in brain inflammation. Modification of NF-κB, TNF-α, visfatin and adiponectin has been shown to cause these effects. Galantamine activates the cholinergic anti-inflammatory system, which is one of the most important anti-inflammatory mechanisms in human biology. This pathway is activated by α7 nicotinic acetylcholine receptors and protects the body from chronic systemic inflammation [44]. (α7 nAChR). Galantamine activates the anti-inflammatory effect of cholinergic, which reduces the production of pro-inflammatory cytokine by 50-75 percent. Galantamine reduces systemic inflammation by inhibiting the enzyme acetylcholinesterase, which reduces the degradation of acetylcholine [8,15].

6. **Anti-diabetic action:** Galantamine, on the other hand, has shown a significant decrease in AChE activity in all tissues at its lowest dose, even lower AChE activity in the brain than normal. The n5-STZ model is a well-known model for type 2 diabetes research, with high fructosamine, decreased insulin of the pancreas, and subsequent decrease in basal insulin sources. Low insulin levels for STZ and / or CNS insulinopenia caused by peripheral Interventional radiography can both be suspected of increased weight gain in diabetic rats. Metabolic changes reduce insulin absorption in the BBB, which is triggered by hyperglycemia, which leads to the formation of an unhealthy diet. The effect of insulin on the brain is a basic way to control your diet [45,46]. In another study, rats with low brain insulin and erroneous insulin receptors had dementia [47]. Galantamine, on the other hand, has been found to have a dose-dependent effect on the diet of diabetic rats. Insulin levels are elevated, which activates vagal tone and reduces appetite to [47,48]. Significance of moderate cholinergic transmission in food balance was demonstrated by galantamine stimulation of the presynaptic alpha7 nicotinic acetylcholine receptor (7nAChR). Vildagliptin, on the other hand, had no effect on diet or weight gain. Galantamine activates the presynaptic alpha7 nicotinic acetylcholine receptor (7nAChR), which has a profound effect on central cholinergic signaling and diet regulation [9,49,50]. Galantamine, which has been shown to have central effects, has the ability to reverse glucose homeostasis-related metrics. Obesity and diabetes mellitus cause vagal tone suppression and route disruption. As a result, galantamine's anti-diabetic actions are attributed to its stimulation of the cholinergic pathway (inhibition of AChE as well as an agonist of the 7nAChR and activation of the efferent vagus nerve) [1]. It acts as a neural bridge between the liver, pancreatic cells, and adipose tissue. Insulin secretion, pancreatic -cell mass, energy expenditure modulation, glucose metabolism, hepatic glucose/glycogen synthesis, systemic insulin sensitivity, and fat distribution between liver and peripheral tissues are all influenced [49]. An increase in the phosphorylation of insulin receptors was observed, followed by the activation / phosphorylation of Protein Kinase B (also known as Akt protein) and elevated GLUT2 and GLUT4 (sugar carriers) responsible for increased insulin sensitivity. In another experiment, galantamine was found to lower elevated TGs (triglycerides). Modification of the observed lipid panel [51,52]. It is explained by an increase in insulin imbalance, which is opposed to galantamine. Galantamine can be used as an adjunct to antidiabetic in the treatment of T2DM, according to the results (type 2 diabetes) [1].

7. **Anti-oxidant action:** Galantamine is a natural antioxidant alkaloid. It is a scavenger of active oxygen species that protects neurons by preventing oxidative damage. The antioxidant effects of Galantamine Hydrobromide were investigated using an in-vitro luminol-based chemiluminescence method. The ability of galantamine and galantamine Hydrobromide to remove active oxygen species such as • Oβ-, • OH, and HOCl depends on the enol group in the molecule. The amount of compound resulting from the extinction of active oxygen species should be affected by any chemical modification of the enol group; the intensity of the extraction action is reduced by system O_2–> HOCl> • OH [1]. When galantamine is converted to galantamine Hydrobromide, the effect of excessive detoxification increases dramatically [53]. The radical scavenging activity is not affected by quaternary coordinated positive nitrogen, although it is responsible for enhancing the disposal effect. The antioxidant activity of galantamine is enhanced by the presence of the enol group and quaternary nitrogen [54]. These findings support and demonstrate the antioxidant properties of galantamine.

Galantamine studies

The table below shows the results of several galantamine research projects Table 2;

Table 2: Studies on Galanthamine [1]

S.No.	Studies on the brain	Findings
1.	Influence on dopamine-regulated behavior and cholinergic networks in rats.	The subcutaneous dose of apomorphine 1 mg / kg has caused behavioral changes such as increased licking and odor. GAL injections significantly inhibited these changes.
2.	Model nucleusbasalis magno cellularis lesions	Significant decrease in choline acetyltransferase activity, as well as local memory deficiency [55]
3.	A swim-maze test paradigm was developed to test local memory ability in mice with NBM lesions	GAL is delivered with improved performance intraperitoneally in a timely manner. A U-swim-maze test, containing 2 mg / kg GAL that provides the best dose response [55]
4.	Testing in mice with NMB lesions.	Improved performance [56]
5.	Scopolamine-induced passive avoidance test	GAL injection greatly lowers scopolamine-induced learning and memory impairments and inhibits scopolamine-induced passive avoidance [57]
6.	GAL's allosterically altering ability to nAChR in young and old rabbits has been investigated	Essential control of the nicotinic environment; evidence of GAL tolerance and attenuation receptor up regulation [58]

Tolerance and safety

Galantamine is generally considered to be a well-tolerated and safe drug. Only 14 percent of study participants withdrew due to adverse events, according to a meta-analysis of large placebo-controlled clinical studies [59]. The most common side effects include symptoms such as nausea (24%), vomiting (14%), diarrhea (8%), abdominal discomfort, dyspepsia, anorexia, and weight loss (10%), all caused by cholinergic-dependent activity. These side effects are most common during the initial phase of treatment with increasing doses, and usually go away over time Dizziness (10%), confusion, dizziness, insomnia, and headache are all documented, as are urinary tract infections and - in rare cases - severe Bradycardia [3,59]. Galantamine can prolong QT time and produce arrhythmia [60], so people with pre-existing heart symptoms should use it with caution. Hypertension, transient ischemia episodes, tinnitus, depression, fever, and asthenia have all been reported more frequently under galantamine than under placebo, according to product reviews of Reminyl [61]. Bullous pemphigoid case developed after galantamine treatment has recently been reported [62]. Galantamine in the formation of extended secretion appears to reduce the duration of abdominal symptoms but not the frequency of all [63].

Significant negative side effects

Galantamine has a long list of serious side effects, according to the FDA. Allergic reactions are called (rash, rash or itching), trouble with breathing or swallowing, feeling of tightness in the chest, mouth, face, lips, or swelling of the tongue. Bloody, dark, or drunk stools, numbness, burning, or itching, confusion, chest tightness, difficult or painful urination, fever, fainting, hallucinations, mood swings or mood swings, new or worsening symptoms, and other side effects should be avoided. . Be sure to talk to your doctor about any side effects.

Dosage

Galantamine is used in Europe for those with moderate to severe dementia Alzheimer's disease. The medicine should be taken twice a day, preferably for breakfast and dinner 8 mg / day for 4 weeks the recommended first dose. At least 4 weeks, the initial dose is 16 mg / day [64]. After this time, an increase in the recommended dose adjustment of 24 mg / day may be evaluated, varying from person to person depending on clinical benefit and tolerability [65]. Galantamine is used to treat severe liver disease (Child Pugh Score> 9) and kidney (creatinine clearance 0.54 L / h) disorders. In patients with severe liver failure, treatment should begin with a dose of 4 mg per day, which is given accordingly at breakfast. The dose can be increased to 4 mg twice daily after 4 weeks of previous treatment for at least 4 weeks. The dose can be increased to 8 mg twice daily. There is no need to change the dose in people with mild liver failure or those with a creatine clearance of 0.54 L / h [2].

Drug interactions

Galantamine suppresses AChE, so interactions with drugs that affect the cholinergic system are possible. As a result, the drug inhibits the activities of anticholinergic drugs (no further details are available). Pharmacodynamic interactions are considered when digoxin and blockers are combined. However, galantamine 12mg twice daily did not show any effect on the pharmacokinetics of digoxin or warfarin. Galantamine is expected to enhance the effect of succinylcholine on muscle relaxation during anesthesia. Galantamine is made up of CYP2D6 and CYP3A4, so strong

inhibitors of these isoenzymes can enhance the cholinergic effects of the drug, including adverse events (e.g., nausea and vomiting). When galantamine is combined with paroxetine (CYP2D6 inhibitor), ketoconazole, or erythromycin (both CYP3A4 inhibitors), its bioavailability increases by 40%, 30%, and 12%, respectively [64].

Conclusion

Galantamine is an acetylcholinesterase inhibitor with a long history of use to reverse the effects of neuromuscular blockade. Galantamine is not only an alternative medicine for Alzheimer's disease, but it also has many other benefits such as antidiabetic, anti-inflammatory, and antioxidant effects. Biological research on galantamine has shown various beneficial, therapeutic, and protective effects on organ systems. Therefore, galantamine is a phytochemical with a variety of pharmacological properties that need to be re-investigated in order to establish an effective safety profile in humans and to obtain therapeutic benefits.

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