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Review Article

A Review on Pharmacological Potential of Galantamine

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ABSTRACT

Introduction: Galantamine a traditional herb has also been explored for a number of pharmacological effects. Today, galantamine has been observed for its nootropic effect. **Methodology:** The objective of this review is to study the evidence of effectiveness and pharmacological effects of galantamine. The preclinical and randomized controlled clinical trials pertaining to studies of galantamine are included. Chemical properties of galantamine and its structure activity relationship pertaining to various biological activities has also been documented. **Result and Conclusion:** The review revealed protective effects of galantamine on functions and integrity of liver, brain and memory impairment. The various independent studies have demonstrated anti-alzheimer, antioxidant, antidiabetic and neuroprotective effect of galantamine. The present review highlights current information and health-promoting effects of a traditionally known drug galantamine.

Key words: Anti-alzheimer, Anti-diabetic, Nootropic, Neuroprotective, Galantamine.

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INTRODUCTION

Galantamine hydrobromide is a tertiary alkaloid which belongs to the Amaryllidaceae family.[1] It has been isolated from many species including *Leucojum*s species, *Narcissus* species and *Galanthus* species. The drug has a long history of use and now it has become an important therapeutic option in various diseases. The pharmacological history of galantamine shows that the bioactive compound was discovered accidentally in the early 1950s and the plant extracts were initially used to treat nerve pain and poliomyelitis.[2] The development of galantamine as a clinically used drug started in early 1950s. According to reports a Russian pharmacologist discovered that local villagers living at the foot of Ural Mountain used wild Caucasian snowdrop to treat an aliment considers to be poliomyelitis in children.[3] Later in 1951 a study demonstrated AChE inhibiting properties of Galantamine and its antagonizing effects on curare action.[4] Further in 1952 Galantamine was first isolated from *Galanthus woronowii* perennial herbaceous plants in the family Amaryllidaceae.[5] In 1956/7 alternative sources of galantamine including the leaves of *Narcissus* spp. and *Galanthu snivalis* family Amaryllidaceae as as well as *Leucojum aestivum* (the main source of galantamine in the Eastern European countries until its introduction onto the Western pharmaceutical market) were suggested.[6,7] Late 1950s various pre-clinical studies on the pharmacology of Galantamine were carried out. The antagonistic effects of galantamine against non-depolarizing neuromuscular blocking agents (shown in experiments on neuromuscular preparation of cats *in situ* in experiments *in vitro* on frog rectus abdominis muscle, etc) were some of the pre-clinical studies. Galantamine was registered under the trade name "NIVALIN" and was commercially available in Bulgaria. The first data on anti cholinesterase activity of Galantamine was reported in early 1960s from an *in vivo* study in an anaesthetized cat.[8] Later on pre-clinical development begin and researchers searching for novel treatments of Alzheimer's disease started investigating the therapeutic effects of galantamine.[9-11] Galantamine was approved for Alzheimer's by 1990s. Sanochemia Pharmazeutika obtained the first patent on the synthetic process of galantamine in 1996 and Galantamine got its first approval of license in Iceland, Ireland, Sweden and UK for the treatment of Alzheimer's disease.[12-14] Currently Galantamine has been approved in the United States, many European countries and some Asian countries as a drug of choice for Alzheimer's disease.It is a clinically approved drug for the treatment of Alzheimer disease which acts as a CNS AChE inhibitor and allosteric potentiating ligand of the neuronal cholinergic nicotinic receptors.[15] It also has significant anti-inflammatory[16] and antioxidant[17] effects. Furthermore, in 2009, it has reported to have use in antidiabetic therapy.[18]

Structure elucidation of galantamine

Galantamine has got a 3D complex structure with an unanticipated orientation of the ligand at the active site and remarkable protein-ligand interactions seen in its X-ray structure at 2.5A resolution.[19] It binds at the base of the active site by interacting with the acyl-binding pocket as well as the principal quaternary ammonium-binding site, yet the tertiary amine group of galantamine has no direct interaction with Trp84 (Figure 1).[20]

Pharmacokinetics of galantamine

The drug has Bioavailability of about 90% and it shows dose dependent effect on pharmacokinetics. The volume of distribution is large and has low protein binding of 28.3-33.8%. Metabolism is via cytochrome P450 system, specifically through CYP2D6 and CYP3A4 isoenzymes. It appears 20-25% unchanged in the urine.[21]

Mechanism of action: Dual action of galantamine

Galantamine has a dual mechanism of action on the cholinergic system—it allosterically modulates nAChR and inhibits ACh. It has a pKa of 8.32 and a 53-fold greater selectivity for human erythrocyte AChE than plasma BuChE (AChE IC_{50} = 0.35nM; BuChE IC_{50} = 18.6nM). Also, it demonstrates a 10-fold lower potency for human brain AChE than for the red blood cell variant.[22] GAL potentiates nicotinic neurotransmission by allosteric modulation on nAChR GAL binds to both pre-and post-synaptic nAChR on cholinernergic neurons, but uses a different binding site to the one used by ACh. When GAL and Ach bind simultaneously to their respective binding sites, the response of nAChR is amplified (Figure 2).[23] Since pre-synaptic nAChR also mediate ACh release, allosteric modulation of these receptors would be expected to increase the release of Ach. Activation of pre-synaptic nAChR also increases the

release of other neurotransmitters thought which might play an important part in memory, similar to glutamate .Therefore, by potentiating nicotinic neurotransmitter, modulation of nAChR may produce important clinical benefits in Alzheimer's disease (AD), which includes delaying deterioration in patient functioning. Other than potentiating nicotinic neurotransmitter, Galantamine GAL also increases the availability of Acetylcholine (Ach) in the cholinergic synapse by competitively inhibiting the enzyme AChE, responsible for its breakdown. The binding of GAL to AChE slows down the catabolism of ACh and, as a consequence ACh levels in the synaptic cleft are increased.[24] GAL has a more than 10-fold selectivity for AChE compared with BuChE, which is in contrast to non-selective agents such as tacrine and physostigmine. Although the precise clinical relevance of the selectivity for AchE is not known.

The *in vivo* and *in vitro* studies found that the inhibition of AChE ceases within 24 hr of discontinuing GAL, indicating that anesthetic agents and muscle relaxants can be administered safely within a short period after discontinuing GAL.[25]

Adverse events associated Galantamine treatment

The adverse events of GAL were recorded, which were mild to moderate in severity and predominantly gastrointestinal symptoms. Nausea is the most commonly reported event with GAL. Less frequently it showed muscular weakness. Most adverse events reported are mild to moderate in severity and the proportion of serious adverse events was comparable. Some of the ADR were gastrointestinal symptoms with mild severity.[26]

Studies on galantamine

The following table illustrates the various studies performed on galantamine. Table 1.

Table 1: Studies on galantamine

Neurological studies	Findings
Influence on central cholinergic pathways and on dopamine-regulated behavior in rats.	The subcutaneous injection of 1 mg/kg apomorphine induced changes in behavior, such as increased licking and sniffing. These changes were significantly reduced by GAL injections were significantly reduced by GAL injections.
Nucleusbasalis magno cellularis lesions model	Significant reduction in choline acetyltransferase activity and deficits in spatial memory.[27]
swim-maze test model to assess spatial memory performance in NBM-lesioned mice	Intraperitionally administered GAL improved Performance in a time-dependent manner. An U-swim-maze test, with the optimal dose response occurring with 2 mg/kg GAL.[27]
Passive avoidance test on NMB-lesioned mice	Improved performance.[28]
Scopolamine -induced passive avoidance test	GAL injection significantly reduces scopolamine induced learning and memory deficits, as well as inhibited scopolamine induced passive avoidance.[29]
Investigation of ability of GAL to allosterically modulate nAChR using young and older rabbits	Significant up-regulation of nicotinic sites; showed signs of tolerance to GAL and attenuation receptor up regulation.[30]

Galantamine and Alzheimer's disease

Alzheimer's disease is neurodegenerative disorder, a common cause of dementia in aged people. It may be sporadic or may be the result with the involvement of other neuropathological situation includingcerebrovascular disease or cortical Lewy bodies. AD has become a disease of social, economic and medical concern. The histological findings in AD are the presence of intraneuronal neurofibrillary tangles and extracellular neuritic senile amyloid plaques.[32] The exact etiology of AD is not known. In the past few decades therapeutic efforts were made for developing treatment modalities. Central cholinergic transmission is important for cognition which came forth as undeniable evidence, the cholinergic neurons and pathways are disrupted in AD. Cholinergic replacement therapy thus is a cogent approach for the treatment of the disease. The findings suggested that inhibitor of AChE could be the therapeutic solution[33]. Galantamine emerged as a drug of choice for patients with moderate to severe AD. The findings suggested that galantamine is effective for such common forms of dementia *viz.* vascular dementia and Alzheimer's disease with cerebrovascular disease. Hence, galantamine is accepted and marketed as the drug of choice for AD.[34]

Galantamine in brain

Galantamine is the introduced aspect for the association of cholinergic neurons in biological phenomenon since it is an inhibitor of acetylcholinesterase and has allosteric actions on nicotinic receptors. This property of galantamine has provided a speculative to assess the role of α7NR in the actions of kynurenic acid since the antagonistic effect of kynurenic acid over NMDA (N-methyl-D-aspartate Receptor) and other glutamate receptors is being studied since decades.[35] Many studies have failed to reveal antagonism by kynurenic acid at nicotinic sites, except possibly at concentrations similar to, or higher than, those at which it blocks NMDARs.[36] Although galantamine is not completely precise in its actions, it has been shown to facilitate the activation of NMDA receptors aid in potentiation of 'depolarization' produced by NMDA. The biological effects of which can be blocked by their respective antagonists. However, simultaneous nicotinic receptor 'activation' is a critical issue.[37] The agonistic effect on NMDA receptor is responsible to converse the behavioral effects produced by NMDA receptor antagonists. It was reported that Galantamine an aid LTP (long-term potentiating), a phenomenon dependent on the activation of NMDA receptors, in the presence of a nicotinic receptor blocker, MLA (methyllycaconitine) .These reports in line with previous studies confirm that galantamine can facilitate LTP`,[38] even in the absence of activation of nicotinic receptor

AntiDiabetic effect of Galantamine

Diabetes mellitus is closely associated with cognitive dysfunctions and CNS abnormalities but the exact role in pathophysiology is not known. In a study, the antdiabetic effect of galantamine in n5-STZ model has shown hyper activated AChE enzyme in brain, liver and muscle tissues

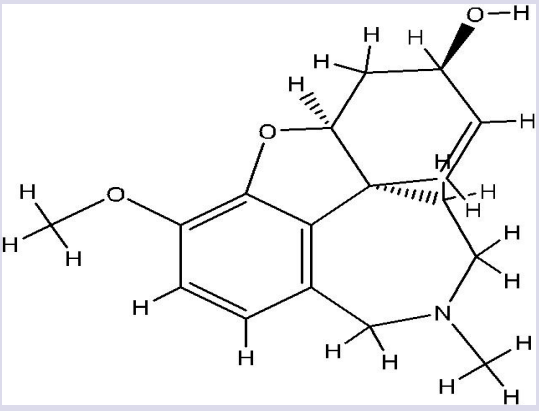

Figure 1: Structure of galantamine.

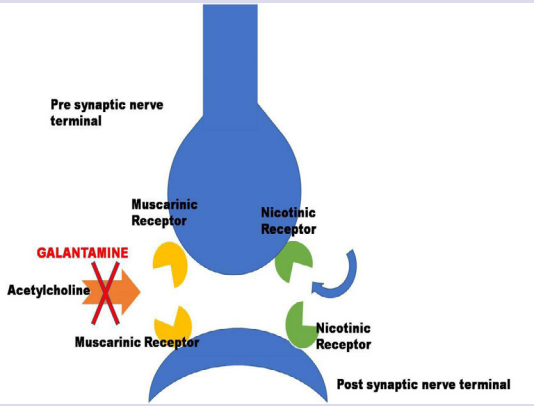

Figure 2: Mechanism of action of Galantamine.

of the diabetic rats. The level of the enzyme was reduced by galantamine in all the tissues. In contrast, vildagliptin (an anti-diabetic agent) showed a slight but noteworthy reduction in the cerebral enzyme. Since vildagliptin has no permeability to BBB (Blood Brain Barrier), yet Glucagon-like peptide-1 (GLP-1) can reach the brain to act as the effector molecule that decreases the AChE activity, possibly *via* activating its central receptor.[39,40] Contrarily galantamine showed a marked decrease in AChE activity in its sub-maximal dose in all tissues and even lower AChE activity in the brain than the normal level. The n5-STZ model is a classic model for the study of type to diabetes mellitus showing elevated fructosamine, reduced pancreatic insulin and stores are subsequent fall of basal insulin Accentuated weight gain witnessed in the diabetic rats, can be attributed to the STZ-induced low insulin level and/or to the CNS insulinopenia mediated by the peripheral Interventional radiography. The metabolic change reduces insulin uptake at the BBB which is distorted in hyperglycemic resulting in uncontrolled food intake. The affect of insulin in the brain is an elementary action in regulating the food intake.[41,42] Another study showed that low brain insulin concentration and impaired insulin receptor has been associated with cognitive deficit in rats.[44] In contrast,was reported that galantamine had dose dependent action to decrease the intake of food in diabetic rats. The insulin level was improved which in turn stimulated the vagal tone which decreased the appetite.[43,44] The galantamine stimulated presynaptic alpha7 nicotinic acetylcholine receptor (α7nAChR) showed the significance of the central cholinergic signaling in controlling food intake. On the other hand, in case of vildagliptin it had no effect on food intake nor weight gain. Galantamine stimulates presynaptic alpha7 nicotinic acetylcholine receptor (α7nAChR) which has significant effect on central cholinergic signaling in controlling food intake.[45-47] Vildagliptin it had no effect on food intake nor weight gain.[48] As established with galantamine to have central effects, it can revert the glucose homeostasis-related parameters. The suppression of vagal tone and dysfunctioning of pathway is seen in obesity and diabetes mellitus.[49] Hence, the anti-diabetic effects of galantamine can be said by the stimulation of the cholinergic pathway (inhibition of the AChE as well as an agonist of the α7nAChR and activating efferent vagus nerve).[50] It serves as the neuronal pathway in the cross-talk between liver, pancreatic -cells and adipose tissue. It also modulates insulin secretion, pancreatic -cell mass, energy expenditure regulation, glucose metabolism, hepatic glucose/glycogen production, systemic insulin sensitivity and fat distribution between liver and peripheral tissues.[45] The influence of the two drugs on the insulin signaling was studied in where increase the phosphorylation of insulin receptors followed by activation/phosphorylation of Protein Kinase B (also known as Akt protein) and the elevation of GLUT2 and GLUT4 (glucose transporter) responsible improved insulin sensitivity was seen. In other study it was also seen that increased level of serum TGs (triglycerides) was lowered by galantamine. However, the enhancement of the unbalanced insulin signaling counteracted by galantamine explains the changes in lipid panel observed.[51,52] It was concluded that galantamine can be an add-on drug with antidiabetics for the management of T2DM (type 2 diabetes mellitus).

Antioxidant activity of galantamine

Galantamine is a natural alkaloid having antioxidant properties. It is a scavenger of reactive oxygen species and exerts neuroprotection mainly by inhibition of the oxidative damage. In an experiment, the antioxidant properties of galantaminehydrobromide were accessed using *in vitro* luminol–dependent chemiluminescence method. The capability of galantamine and galantamine hydrobromide to scavenge the reactive oxygen species: •Oβ –,•OH and HOCl is related to the enol group in the molecule. Any chemical transformation of the enol group should affect the ability of the resulting compound to scavenge the reactive oxygen species, the strength of the radical-scavenging effect decreases in the order: O_2–>HOCl>•OH.[53] The changing of galantamine to galantamine hydrobromide is accompanied with a significant increase of the radical scavenging effect.[54] The quaternary coordinated positively charged nitrogen is not involved in the radical scavenging action, but is responsible for the increasing of the strength of the scavenging effect. The presence of enol group and quaternary nitrogen improves the antioxidant activity,[55] which was in galantamine. These findings supported and suggested the antioxidant activity of galantamine.

CONCLUSION

Galantamine is not only the drug of choice for Alzheimer's disease, but also possess many additional properties including antdiabetic, anti-inflammatory and antioxidant activities etc. Biological studies on galantamine have demonstrated various valuable, therapeutic and protective effects on organ systems. Thus, galantamine is phytochemical with multiple pharmacological activities which should be studied extensively to further establish effective safety profile in human to get therapeutic benefits.

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