

ADVANCES IN THE MEDICINAL CHEMISTRY OF NEUROLOGICAL THERAPEUTICS: A COMPREHENSIVE REVIEW

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ABSTRACT:

The aim of the review on neurological tablets and their chemistry is to provide a detailed toxicology and chemical analysis of various pharmaceutical tablets used in management of neurological disorders correlating their molecular structures with their therapeutic efficacy and pharmacokinetic profile. This review enables us to categorize neurological drugs and evaluate therapeutic scope, drug chemistry, structural analysis, pharmacokinetics and the blood brain barrier and mechanism of action. This review was specially focussed on the drug mode of action on particular issue acquired in our body and chemistry behind their results.

KEYWORDS: Neurological disorders, Drug development, Neuropeptides, Blood-brain barrier, Neuropharmacology

INTRODUCTION

Neurologic medicines are classified into disease-specific categories (antimigraine, antiepileptic, and antiparkinsonism) along with essential medicines for infectious and neoplastic diseases. There are other medicines used to treat neurologic disorders that are classified by pharmacologic effect (antihypertensive, anticholinesterase, diuretic, antithrombotic, lipid-lowering medicines)[1].

Ginseng is one of the most widely used herbal medicines in human. Central nervous system (CNS) diseases are most widely investigated diseases among all others in respect to the ginseng's therapeutic effects. These include Alzheimer's disease, Parkinson's disease, cerebral ischemia, depression, and many other neurological disorders including neurodevelopmental disorders. Not only the various types of diseases but also the diverse array of target pathways or molecules ginseng exerts its effect on. These range, for example, from neuroprotection to the regulation of synaptic plasticity and from regulation of neuroinflammatory processes to the regulation of neurotransmitter release, too many to mention. In general, ginseng and even a single compound of ginsenoside produce its effects on multiple sites of action, which make it an ideal candidate to develop multi-target drugs.

This is most important in CNS diseases where multiple of etiological and pathological targets working together to regulate the final pathophysiology of diseases. In this review, we tried to provide comprehensive information on the pharmacological and therapeutic effects of ginseng and ginsenosides on neurodegenerative and other neurological diseases. Side by side comparison of the therapeutic effects in various neurological disorders may widen our understanding of the therapeutic potential of ginseng in CNS diseases and the possibility to develop not only symptomatic drugs but also disease modifying reagents based on ginseng.

The blood-brain barrier (BBB) and its penetration by neurotherapeutics was the subject of a recent issue of this journal [2]. This series of articles primarily had a biological orientation. From a medicinal chemical perspective, the ability to design drugs capable of penetrating the BBB and effecting the desired biological response is a formidable challenge.

In the broadest sense, moderately lipophilic drugs cross the BBB by passive diffusion and the hydrogen bonding properties of drugs can significantly influence their CNS uptake profiles. Polar molecules are generally poor CNS agents unless they undergo active transport across the CNS. Size, ionization properties, and molecular flexibility are other factors observed to influence transport of an organic compound across the BBB [3].

Neurological disorders

Neurological disorders are conditions that affect how your nervous system functions. This involves your central nervous system and peripheral nervous system. There are hundreds of neurological disorders like Alzheimer's disease, multiple sclerosis and meningitis, for example they cause symptoms that affect how you move, think and feel. Treatment options vary based on their type. These disorders also cause physical, cognitive, emotional and behavioral symptoms like pain, confusion, mood changes and coordination difficulties.

Neurological tablets

Neurological tablets are solid pharmaceutical dosage forms produced by compressing or moulding APIs and excipients classified into types like compressed, coated (film/sugar), enteric coated , buccal / sublingual, Effervescent and chewable. Production primarily uses wet granulation, dry granulation, or direct compression with key stages including weighing, mixing, granulation compression and coating. Neurological tablet is an active ingredient composed of different types of inactive ingredients. Inactive ingredient is also called as Excipient. mixture of inactive ungriclient is an ingredient. - drug /API

Composition

Active ingredient	Inactive ingredients
Neurological tablet	Binders
	Disintegrates
	Lubricants
	Gladients
	Diluents
	Solvents
	Preservatives
	Sweetening agents
	Buffers
	Flavouring agents
	Colouring agents

Neurological drug

Neurological drugs are pharmaceutical agents targeting the CNS to treat disorders like Parkinson's, Alzheimer's, epilepsy, seizures and migraines . They modulate neurotransmitters (dopamine, GABA) and ion channels, often requiring small hydrophobic molecules to cross the blood brain barrier.

Drugs often prescribed by neurologists include:

- Anticonvulsants, or antiepileptic drugs: prevent /treat abnormal electrical activity in the brain. Many people have active epilepsy, and lots of the common drugs prescribed by neurologists treat epilepsy or similar disorders. Drugs to treat patients with dementia or Parkinson's disease. Antidepressants, beta blockers, and blood thinners

[4].

- The classification of neurological medications (often called CNS or Central Nervous System agents) is typically organized by the condition they treat or their chemical mechanism. Because "neurology" is a broad field, these drugs range from daily controllers for epilepsy to emergency treatments for stroke. Below is a classification of common neurological tablets and their respective drugs.

Anticonvulsants (Anti-Seizure Drugs)

These are used to stabilize electrical activity in the brain to prevent seizures. Many are also used "off-label" for nerve pain or mood stabilization.

Drug sub-class

Common Generic Drugs

- | | |
|----------------------------|----------------------------|
| • Broad Spectrum. | Levetiracetam, valproate |
| • Sodium channel blockers. | Carbamazepine, Lamotrigine |
| • GABA Analogs. | Gabapentin, Pregabalin |
| • Others. | Topiramate, Lacosamide |

Antiparkinsonian Agents

These drugs aim to either increase dopamine levels in the brain or block acetylcholine to manage tremors and rigidity.

- **Dopaminergic Agents:** Carbidopa-Levodopa (Sinemet) - the "gold standard."
- **Dopamine Agonists:** Pramipexole (Mirapex), Ropinirole (Requip).
- **MAO-B Inhibitors:** Selegiline (Eldepryl), Rasagiline (Azilect).
- **Anticholinergics:** Trihexyphenidyl (Artane), Benztropine (Cogentin).

Antidementia Agents

- Used primarily for Alzheimer's disease to improve cognitive function and slow memory decline.
- **Cholinesterase Inhibitors:** Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razadyne).
- **NMDA Receptor Antagonists:** Memantine (Namenda).
- **Combination:** Donepezil/Memantine (Namzaric).

Antimigraine Medications

- Migraine treatment is split into two categories: Abortive (to stop an active headache) and Prophylactic (to prevent them).

Abortive (Acute)

- **Triptans:** Sumatriptan (Imitrex), Rizatriptan (Maxalt), Zolmitriptan (Zomig).
- **Gepants (CGRP Antagonists):** Rimegepant (Nurtec ODT), Ubrogepant (Ubrovelvy).
- **NSAIDs:** Naproxen (Aleve), Diclofenac (Cataflam).

Prophylactic (Preventive)

- **Beta-Blockers:** Propranolol (Inderal).
- **Anticonvulsants:** Topiramate (Topamax)
- **Antidepressants:** Amitriptyline (Elavil).

Neurovascular & Stroke Prevention

- These focus on maintaining blood flow to the brain and preventing clots.
- **Antiplatelets:** Aspirin, Clopidogrel (Plavix). **Anticoagulants:** Warfarin (Coumadin), Apixaban (Eliquis), Rivaroxaban (Xarelto).
- **Statins:** Atorvastatin (Lipitor) used for neuroprotection and stroke risk reduction.

Psychotropic & Neuromuscular Agents

- **Anxiolytics/Sedatives:** Diazepam (Valium), Lorazepam (Ativan), Alprazolam (Xanax).
- **Muscle Relaxants:** Baclofen (Lioresal), Tizanidine (Zanaflex).
- **CNS Stimulants (for ADHD/Narcolepsy):** Methylphenidate (Ritalin), Amphetamine salts (Adderall).

GABA PENTININ: Anti convulsants

Gabapentin is a versatile medication that has evolved from a specific anti-seizure drug into a widely used treatment for various chronic pain and neurological conditions. While it is structurally similar to the neurotransmitter GABA, it does not actually bind to GABA receptors. Instead, it works by modulating calcium channels to dampen "hyper-excited" neurons.

- **IUPAC NAME:** 2- [1-(AMINO METHYL) CYCLO HEXANE] ACETIC ACID
- **MOLECULAR WEIGHT:** 171.24g/mol

- COMMERCIAL NAME (Tablet): NEURONTIN
- PHYSICAL APPEARANCE: WHITE TO OFF WHITE CRYSTALLINE SOLID
- MELTING POINT: 162 - 166 °C
- SOLUBILITY: FREELY SOLUBLE IN
 - a. Water
 - b. Alkaline
 - c. Acedic solutions



fig.1.1(a).

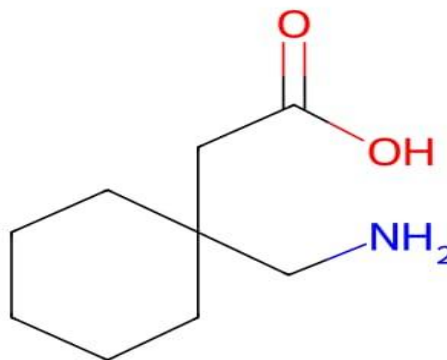


fig.1.1(b)

3.1.1 structural elucidation

Gabapentin is a structural analogue of the neurotransmitter GABA (γ -aminobutyric acid). Its chemical name is 1-(aminomethyl)cyclohexanecarboxylic acid.

Core: A cyclohexane ring.

Substituents: Both an aminomethyl group and a carboxymethyl group are attached to the same carbon atom (C1) of the cyclohexane ring.

Classification: It is a 1,1-disubstituted cyclohexane derivative.

3.1.2 synthesis of gabapentin

The chemical synthesis of Gabapentin, a medication primarily used to treat seizures and nerve pain. The process starts from a cyclic anhydride and proceeds through two main chemical transformations.

1. Formation of the Monoamide

The starting material is 1,1-cyclohexane diacetic acid anhydride.

- **Reagent:** Ammonia (NH₃)
- **Reaction:** The ammonia acts as a nucleophile, attacking one of the carbonyl carbons of the cyclic anhydride. This breaks the C - O bond of the anhydride ring.
- **Product:** One side becomes a carboxylic acid (-COOH) and the other becomes a primary amide (-CONH₂), forming 2-(1-(carbamoylmethyl) cyclohexyl)acetic acid.

2. Hoffmann Rearrangement

The intermediate monoamide is then converted into the final product.

- **Reagent:** Sodium hypobromite (NaOBr) in Sodium hydroxide (NaOH).
- **Reaction:** This is a classic Hoffmann Rearrangement (often spelled "Hoffmann" in some texts). The reaction converts a primary amide into a primary amine with the loss of one carbon atom (as CO₂).

Mechanism:

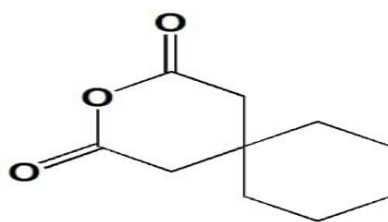
The amide (-CONH₂) reacts with NaOBr to form an N-bromoamide.

Base-catalyzed deprotonation and rearrangement lead to an isocyanate intermediate.

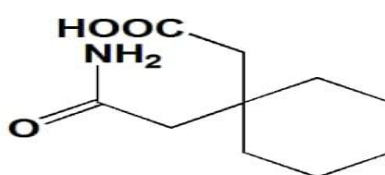
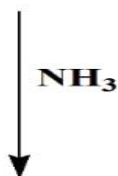
Hydrolysis of the isocyanate yields the primary amine (-CH₂NH₂).

Final Product: Gabapentin

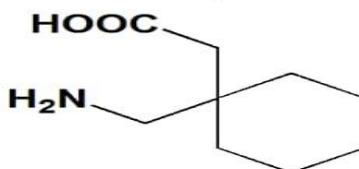
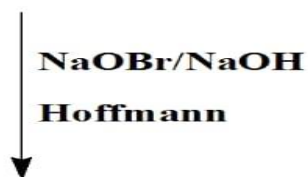
The resulting molecule is Gabapentin. It is a structural analogue of the neurotransmitter γ -aminobutyric acid (GABA), though it has a different mechanism of action. It is characterized by the cyclohexane ring with two substituents at the same carbon: an acetic acid group and a methylamine group.



1,1-cyclohexane diacetic acid anhydride



2-(1-(carbamoylmethyl)cyclohexyl)acetic acid



Gabapentin

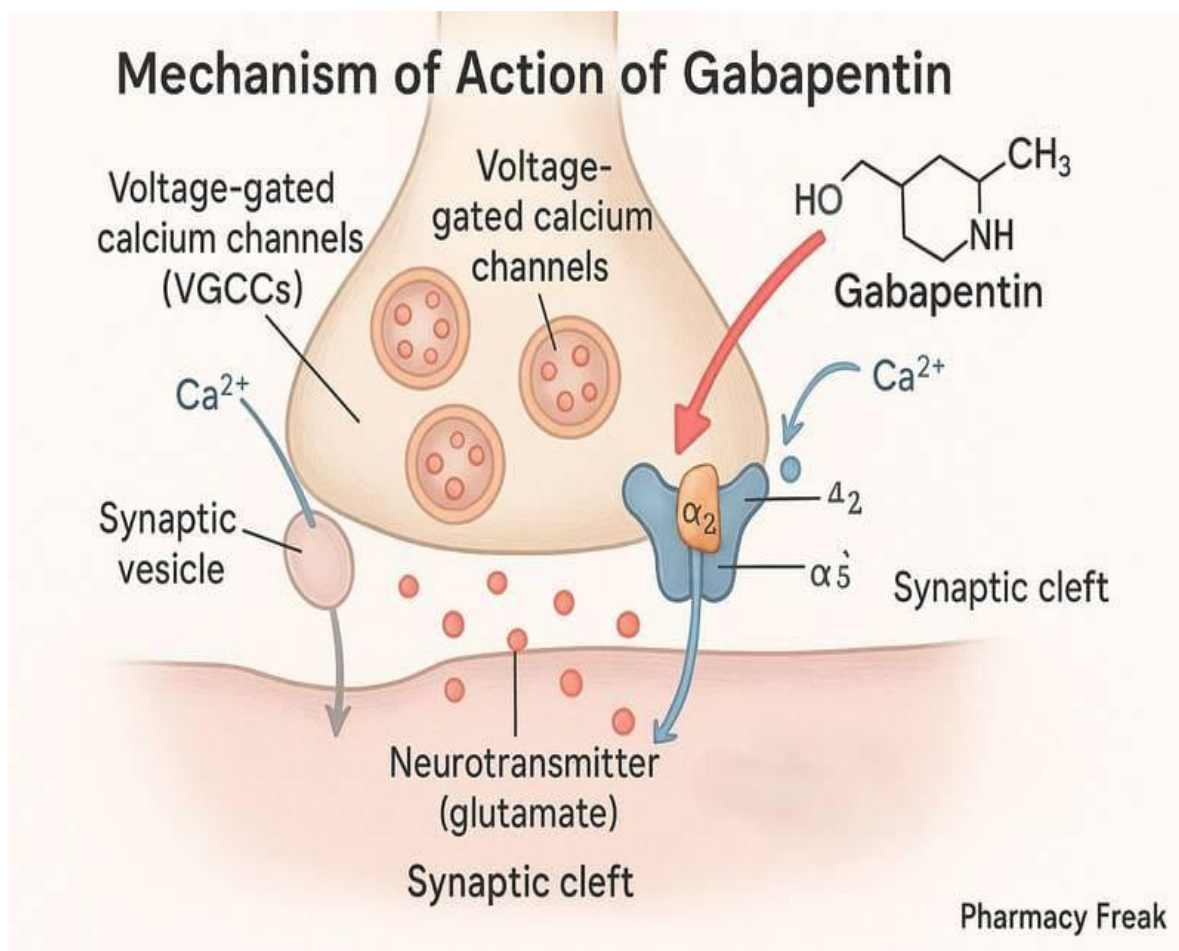
3.1.3 Mode of Action

within the CNS, the presynaptic neurons are loaded with neuro transmitters such as glutamate and on the post synaptic neurons receptors such as AMPA are Existing which are responsible for fast Excitatory potential. These AMPA Receptors are coupled with sodium channels resulting in fast excitatory post synaptic potential. But for this excitation, glutamate should be released which is initiated by calcium-mediated exocytosis. So these calcium channels play an important role on the presynaptic neurons.

Now when calcium enters into the presynaptic neurons, it produces exocytosis and the glutamate can act on AMPA Receptors so that now these sodium channels are activated and sodium can enter into the post synaptic neurons. In this way the chemical signal is transmitted from presynaptic neurons to the post synaptic neurons, now these post synaptic neurons are activated to produce CNS excitation so in the epilepsy, these neurons are repeatedly excited resulting in asynchronous neuronal discharge leading to scizures in the patients.

But for the activation of these calcium channels on the presynaptic neurons, one of the subunit is present that is alpha 2 delta 1 sub unit, this sub unit facilitates expression of the calcium channel pores through which calcium can enter.

Now Gabapentin is one of the drug which can block this alpha 2 delta 1 site on the voltage gated calcium channels such that it can inhibit this activity so when these channels are inhibited, calcium cannot enter resulting in inhibition of exocytosis and post synaptic activation. In this way Gabapentin can reduce the neuronal activity by inhibiting the neurotransmitter release. It is not directly acting on voltage gated calcium channels but it is going to bind to Alpha 2 delta 1 site where it blocks the expression of calcium channel pores within the presynaptic neurons.



Pharmacodynamics

Gabapentin can cross the blood–brain barrier and enter the central nervous system. Gabapentin concentration in cerebrospinal fluid is approximately 9–14% of its blood plasma concentration. Due to its low lipophilicity, gabapentin requires active transport across the blood–brain barrier. The LAT is highly expressed at the blood–brain barrier and transports gabapentin across into the brain. As with intestinal absorption mediated by an amino acid transporter, the transport of gabapentin across the blood–brain barrier by LAT is saturable. Gabapentin is generally safe in people with liver cirrhosis. Gabapentin is eliminated renally in the urine. It has a relatively short elimination half-life, with the reported average value of 5 to 7 hours. Because its short elimination half-life, gabapentin must be administered 3 to 4 times per day to maintain therapeutic levels.

3.2 carbidopa - levodopa: antiparkinsonian agents

Carbidopa-levodopa is widely considered the "gold standard" treatment for managing symptoms of Parkinson's disease and parkinsonism. It works by addressing the shortage of dopamine in the brain.

CARBIDOPA

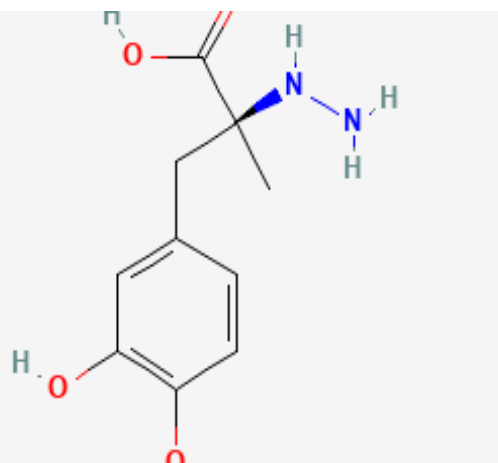
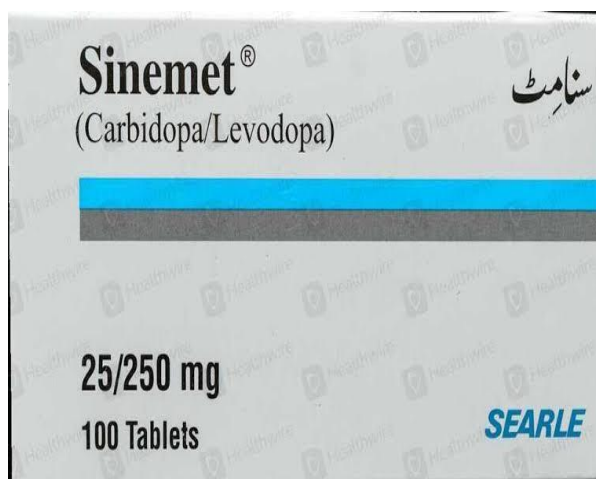
- IUPAC NAME: (2S)-3-(3,4-dihydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid
- MOLECULAR WEIGHT: 226.3 g/mol

LEVODOPA

- IUPAC NAME: (2S)-2-amino-3-(3,4-dihydroxyphenyl)propanoic acid
- MOLECULAR WEIGHT: 197.2 g/mol

Note: They are often used together in a 1:4 or 1:10 ratio in tablet formulations

- COMMERCIAL NAME: Sinemet
- COMBINED MOLAR MASS: 423.4 g/mol



3.2.1 structure elucidation

The structure of Carbidopa and Levodopa (L-DOPA) is a classic exercise in medicinal chemistry. Both molecules are derivatives of the amino acid tyrosine and share a catechol nucleus, but their structural differences are what allow them to work so effectively in tandem for treating Parkinson's disease.

1. Levodopa (L-DOPA)

Levodopa is the metabolic precursor to dopamine. Its structure is essentially a modified amino acid.

Catechol Ring: A benzene ring with two hydroxyl ($-\text{OH}$) groups at the 3 and 4 positions.

Ethylamine Side Chain: A two-carbon chain connecting the ring to an amine group.

Chiral Center: The α -carbon is chiral. The "L" designation (S-enantiomer) is crucial because only this isomer is biologically active and recognized by transport proteins.

Functional Groups: It contains both a carboxylic acid group ($-\text{COOH}$) and a primary amine ($-\text{NH}_2$).

Chemical Formula: $\text{C}_9\text{H}_{11}\text{NO}_4$

2. Carbidopa

Carbidopa is a peripheral decarboxylase inhibitor. It is structurally very similar to Levodopa, which allows it to "mimic" the drug and bind to the enzyme DOPA decarboxylase, but with two critical modifications that prevent its own metabolism.

α -Methyl Group: The addition of a methyl group ($-\text{CH}_3$) at the α position. This creates steric hindrance, making the molecule more stable against certain enzymatic attacks.

Hydrazine Group: Instead of a primary amine ($-\text{NH}_2$), Carbidopa has a hydrazine group ($-\text{NH}-\text{NH}_2$). This is the "secret sauce"—the hydrazine forms a covalent bond with the pyridoxal phosphate (Vitamin B6) cofactor of the decarboxylase enzyme, effectively "clogging" it.

Chemical Formula: $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_4$

3.2.2 synthesis of carbidopa - levodopa

The synthesis of the Carbidopa-Levodopa combination involves two distinct chemical pathways to produce each active pharmaceutical ingredient (API) individually, followed by a pharmaceutical formulation process to combine them into a single dosage form (such as the brand Sinemet).

1. Synthesis of Levodopa (L-DOPA)

The most famous industrial route is the Monsanto Process, which was the first large-scale application of asymmetric catalysis, earning William S. Knowles the Nobel Prize in Chemistry.

Starting Material: Vanillin or catechol derivatives.

Key Intermediate: An enamide precursor (e.g., α -acetamidoacrylic acid derivative).

Asymmetric Hydrogenation: The critical step uses a chiral rhodium catalyst, such as $[\text{Rh}((R,R)\text{-DiPAMP})]^+$, to hydrogenate the prochiral double bond.

Equation: $\text{R}-\text{CH}=\text{C}(\text{NHAc})\text{COOH} + \text{H}_2 \xrightarrow{\text{Rh-DiPAMP}} \text{R}-\text{CH}_2-\text{CH}(\text{NHAc})\text{COOH}$

This ensures the production of the biologically active L-enantiomer with over 95% enantiomeric excess (ee).

Final Step: Acid hydrolysis to remove the protecting groups (acetyl and methyl ethers) to yield pure L-DOPA.

2. Synthesis of Carbidopa

Carbidopa is an α -methyl amino acid derivative containing a hydrazine group ($-\text{NHNH}_2$) instead of a standard amino group.

Starting Material: L- α -methyldopa (itself a common antihypertensive) or its methyl ester.

Amination/Hydrazination:

The amino group of methyldopa is typically reacted with an aminating agent like chloramine or via an oxaziridine intermediate. A recent efficient method involves reacting L- α -methyldopa methyl ester with 3,3-pentamethylene oxaziridine to form a hydrazino-intermediate.

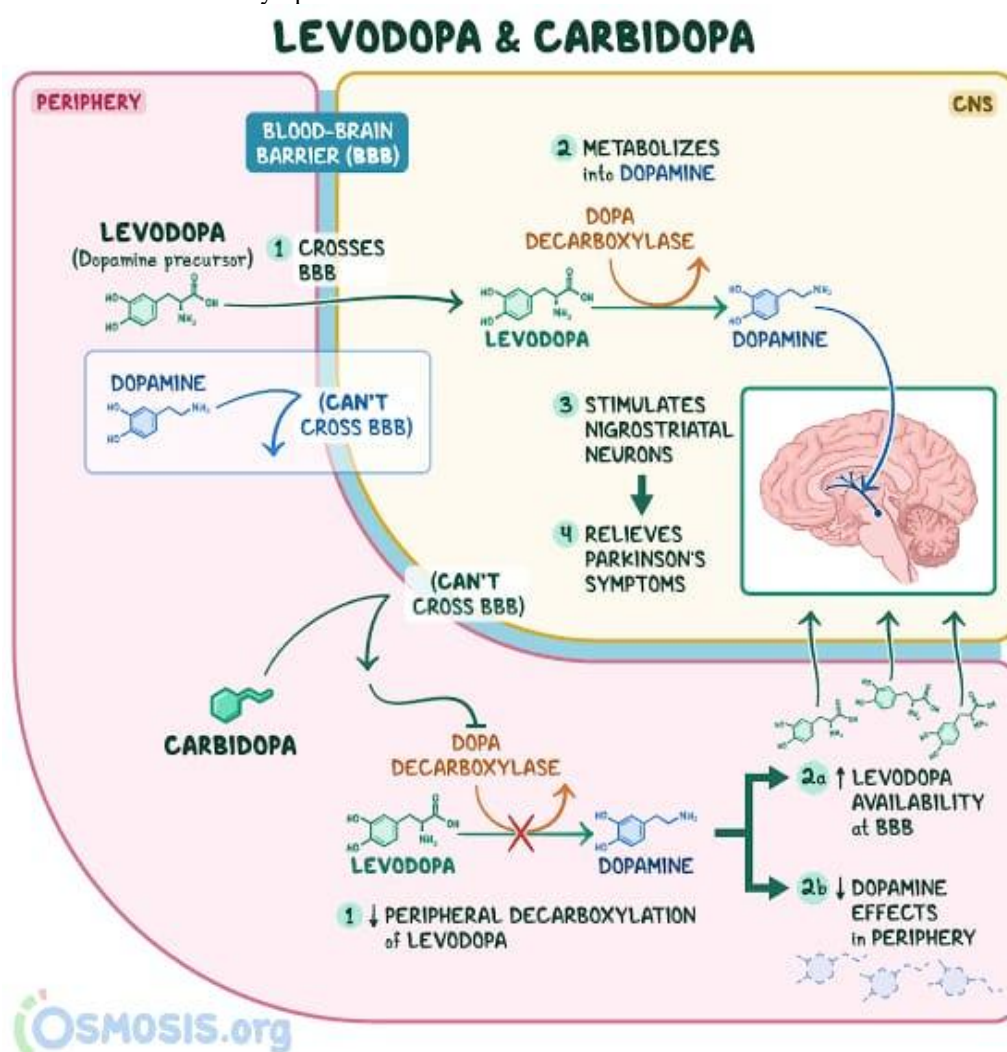
Hydrolysis: The intermediate is then hydrolyzed with a strong acid (like HCl or HBr) to yield the final (-)-(L)-3-(3,4-dihydroxyphenyl)-2-hydrazino-2-methylpropionic acid (Carbidopa).

3. Combination & Formulation

Once the two APIs are synthesized and purified, they are combined in specific ratios—most commonly 1:4 or 1:10 (Carbidopa to Levodopa).

3.2.3 Mechanism of Action

Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it doesn't cross the blood brain barrier. However LEVODOPA the metabolic precursor of dopamine, does cross the blood brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby LEVODOPA relieves symptoms of Parkinson's disease.



The "Protector": Carbidopa is a DOPA decarboxylase inhibitor. Its primary job is to stop the conversion of Levodopa into dopamine in the periphery.

The Barrier: Crucially, Carbidopa cannot cross the BBB. This means it only stops the "wasted" conversion in the body, while leaving the conversion process inside the brain untouched.

Summary of Benefits

By adding Carbidopa to Levodopa (often sold as the combination drug Sinemet), the treatment achieves two major goals:

Feature Effect of Carbidopa

Levodopa Availability **Increases:** More Levodopa stays intact to reach and cross the BBB.

Side Effects **Decreases:** Less dopamine is created in the periphery, reducing nausea and cardiovascular issues.

Therapeutic Effect Increases: Higher levels of dopamine are produced exactly where they are needed—in the brain.

NOTE: This combination is considered the "gold standard" for Parkinson's symptom management, though long-term use can lead to complications like dyskinesia (involuntary movements) or the "on-off phenomenon."

Future of Medications

In neurology, recently developed/or developing medicines are expected for various diseases, including novel migraine therapies, rare neurological diseases, and therapies for Alzheimer's and Parkinson's disease [5].

Precision medicine: Developments such as accelerated genomic discovery are making a new type of medicine, precision medicine. The goal here delivery of optimally targeted and timed interventions that are made specifically for an individual's molecular disease drivers. Neurological diseases are well suited models for precision medicine as growth in our understanding of genetics, phenotypic classification, the development of biomarkers and the potential modifying treatments occurs [6].

For any drug or candidate to achieve optimum therapeutic efficacy, it must possess a high degree of potency and selectivity for interaction with a biological target as well as ability to attain target tissue concentrations that are above a certain threshold value. Absorption, distribution, metabolism, and excretion (ADME) processes play a pivotal role in defining the disposition of a drug candidate, and thus its therapeutic efficacy. Optimizing the chemical structure of lead candidates with respect to the ADME processes has become an integral part of the drug discovery paradigm [7].

Pharmacokinetic properties:

A potential drug's pharmacokinetic properties to a significant extent can be manipulated by the medicinal chemist. However, historically, these properties have not been considered by most medicinal chemists, who in many cases used increases in receptor binding for their optimization strategy. In this section, we briefly look at the pharmacokinetic properties that impact on ADME properties of CNS drugs.

These parameters include: • Metabolic stability • Metabolic liability • Permeability • Protein binding • hERG inhibition

CONCLUSION

Unlike general systemic medications, neurological drugs must be chemically optimized not only for stability and absorption but for the critical task of penetrating the Blood-Brain Barrier (BBB). This review has detailed the complex chemical landscape of pharmaceutical tablets, moving beyond their perception as simple delivery vehicles. The effectiveness of a tablet is fundamentally rooted in the physicochemical properties of its components and the intricate balance between the Active Pharmaceutical Ingredient (API) and its supporting excipient matrix.

The future of neurological tablets lies in prodrug chemistry and nanotechnology. By chemically masking polar groups, we can create prodrugs that remain "invisible" to the BBB's defense mechanisms, only activating once they enter the brain. Furthermore, the development of ligand-targeted tablets suggests a future where medication can be chemically "programmed" to target specific regions of the brain, such as the substantia nigra in Parkinson's patients or the hippocampus in Alzheimer's cases.

In conclusion, the chemistry of neurological tablets is a testament to human ingenuity in the face of biological complexity. By manipulating molecular polarity, ionization states (pKa), and delivery kinetics, pharmaceutical chemistry provides the essential bridge between raw chemical compounds and the restoration of neurological health.

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