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Review Article

IMPORTANCE OF LIPID NANOPARTICLES IN THE TREATMENT OF EPILEPSY: A FOCUS ON NASAL DELIVERY

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ABSTRACT
Nasal delivery of lipid Nanoparticles directly into brain may become an attractive treatment option for epilepsy treatment. High concentration of drug reaches to brain by using lipid Nanoparticles. Nasal delivery bypasses the blood brain barrier and also avoids systemic side effects. This review sets out to discuss brief description about epilepsy, mechanism of epilepsy, drug used in epilepsy and nasal delivery by using lipid nanopariculate carrier for the treatment of epilepsy.
Keywords: Lipid Nanoparticles, epilepsy, intranasal route, liposomes, niosomes

INTRODUCTION

Epilepsy

Epilepsy comes from greek word epilambanin that means seizure or attack.[1] The epilepsies represent a group of brain disorders which have in common the occurrence of spontaneous and recurring epileptic seizures, i.e., hypersynchronous electrical discharges in brain networks. Epilepsy is characterized by recurrent episodes of paroxysmal neural discharge known as seizures. Seizures are a symptom of epilepsy[2]. It is estimated that people suffering from epilepsy face 2-3 times higher mortality as compared to normal population. Seizure related death account for 40 % of all the death due to chronic epilepsy[3].

Classification of Epilepsy

On the basis of Aetiology

- Symptomatic
- Idiopathic
- Presumed symptomatic (“cryptogenic”)[4]

Idiopathic epilepsies

These are generally thought to arise from genetic abnormalities that lead to alteration of basic neuronal regulation.

Symptomatic (or acquired) epilepsies

These arise from the effects of an epileptic lesion, whether that lesion is focal, such as a tumour, or a defect in metabolism causing widespread injury to the brain.

Cryptogenic epilepsies

These involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation. In approximately 40 % of all epilepsy cases, the aetiology is known, including brain insults such as traumatic brain injury (TBI1), ischemic stroke, intracerebral hemorrhage, infections, tumours, cortical dysplasia, several neurodegenerative diseases, and prolonged acute symptomatic seizures such as complex febrile seizures or status epilepticus (SE)

On the basis of seizure

Seizures can be divided into three main catagory

- Generalised seizure
- Partial seizure
- Unknown cause[5]

Partial seizure

Partial seizure is restricted to the distinct area of brain. Normally a particular area of brain is affected.

Generalized Seizure

These seizures originate from both hemisphere of brain concurrently. Generalized seizures are further classified as:

- Absence Seizure: In this type of seizure patient loses consciousness for short duration with few or no symptoms.
- Grand Mal Seizure: In this type of seizure patient loses consciousness and collapses.
- Atonic Seizure: These seizures consist of rapid and general loss of muscle tone for 1-2 seconds.
- Myoclonic Seizure: Myoclonic seizure consists of infrequent jerks that may occur in particular area of body or whole body.
- Tonic Seizure: Tonic seizure consists of stiffening of muscles
- Clonic Seizure: These seizures consist of repetitive and rhythmic jerks that occurs both side of body at the same time.

Unclassified Seizure

These seizures are not classified as partial or generalized seizure type. These seizure takes place in neonates and infants resulted by deviation in neuronal mapping

Table 1: Types of seizure and their subtype

Types of seizure	Sub Type of Seizures
Partial Seizure	• Simple partial (with motor, sensory, autonomic, or psychic signs; consciousness is not impaired) • Complex partial (consciousness is impaired) • Partial seizures evolving to secondarily generalized seizures
Generalized seizures	• Absence (petit mal) • Myoclonic seizure • Clonic seizure • Tonic seizure • Tonic–clonic (grand mal) • Atonic seizure
Unclassified seizures	• Neonatal seizures • Infantile spasms

Aetiology of epilepsy

Epilepsy varies with age but it also depends upon nature and type of seizure. However 50 % cases cause is unknown.

- Infection in brain e.g. meningitis, encephalitis or no supply of oxygen to brain during birth or after a stroke, may produce epilepsy.
- A brain injury, that produces scar tissue, predisposes individuals to developing epilepsy. While it occur after a long duration.
- Neurodegenerative diseases like Alzheimer's diseases may consequences epilepsy.
- Infants/children: congenital malformations, perinatal injuries or hypoxia, developmental neurologic disorders, metabolic defects, injury, and infection are common causes of seizures.
- Young Adults: head trauma, brain tumours, infection and arteriovenous malformations are common cause of epilepsy.
- Elderly: Cerebro vascular disease, CNS degenerative diseases, and brain tumours are common causes.
- Genetics –risk increased 2-3 times in individuals with first degree relative with epilepsy[6].

Pathophysiology of epilepsy has been described as

Disorder in neurnal migration

Abnormal patterns of neuronal migration lead to various forms of agyria or pachygyria whereas lesser degrees of failure of neuronal migration induce neuronal heterotopia in the subcortical white matter. Cortical malformations can both form epileptogenic foci and alter brain development in a manner that diffuse hyper excitability of the cortical network occurs.[7]increases in postsynaptic glutamate receptors and decreases in g-aminobutyric acid (GABA) receptors in microgyric cortex which could promote epileptogenesis.[8]

Genetics of Human Epilepsy

Epilepsies with complex inheritance

Genetic predisposition of absence epilepsy is based on a gene-dependent biochemical derangement leading to increased cortical excitability[9].

Monogenic epilepsy

There are four other monogenic epilepsies;

- Generalized epilepsy with febrile seizures,
- Autosomal dominant nocturnal frontal lobe epilepsy
- Benign familial neonatal convulsions
- Episodic ataxia type 1 with partial seizures) gene defect underlying these epilpesy as these diseases are caused by ion channel mutations.[10,11]

Mechanism involved in epilepsy

Nonsynaptic mechanisms

- Alterations in ionic micro environment; e.g. increased extracellular K^+, decreased extracellular Ca^{++}
- Failure of ion transport: Na^+-K^+ pump or Cl--K^+ co-transport
- Presynaptic terminal bursting
- Ephaptic interactions

Alterations in ionic microenvironment

Repetitive ictal and interictal activity causes increases in extracellular K^+ leading to increased neuronal excitability[12]. Some neurons are very sensitive to changes in membrane K^+ currents, e.g. pyramidal cells in the CA1 region of the hippocampus[13].

Failure of ion transport

Activation of the Na^+-K^+ pump is important for regulation of neuronal excitability during excessive neuronal discharges.[14] Cl--K^+ co-transport mechanism controls the intracellular Cl- concentration and the Cl- gradient across the cell membrane which regulates effectiveness of GABA-activated inhibitory Cl- currents. Interference with this process could cause a

progressive decrease in the effectiveness of GABAergic inhibition leading to increased excitability.[15]

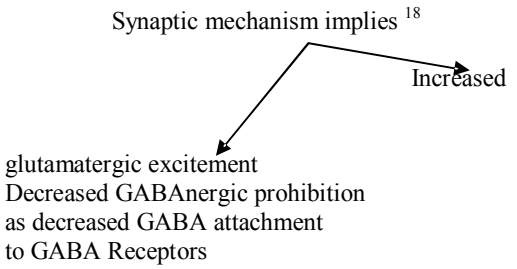
Presynaptic terminal bursting

Abnormal bursts of action potentials occur in the axonal arborizations of thalamocortical relay cells during epileptogenesis. Since one thalamocortical relay cell ends on a large number of cortical neurons, synchronization can occur which might play an important role in interictal-ictal transition.[16]

Ephaptic interaction

Ephaptic interactions are produced when currents from activated neurons excite adjacent neurons in the absence of synaptic connections. Ephaptic effects are strongly dependent on the size of the extracellular space. When extracellular space is small, ephaptic interactions are promoted.[17]

Synaptic mechanism of epilepsy



GABA

GABA play critical role in pathology of epilepsy. Theory behind GABA in epilepsy involves decreased in GABA nergic inhibition result in epilepsy[19]. Inhibitory post synaptic potential causes reduction in amplitude during repetitive activation of cortical circuit. This phenomena might be due to reduction in GABA release from terminal, desensitization of GABA receptor that are conjugated to enhance the Cl^- conductance or alteration in ionic gradient because of intracellular accumulation.[20]

Glutamate

Glutamatergic synapses involve vital purpose in epilepsy mechanism. Activating both ionotropic and metabotropic postsynaptic glutamatergic receptor is proconvulsant. Agonist of NMDA receptor play role in pathology of epilepsy. Enhanced sensitivity of glutamate at NMDA receptor is seen in hippocampal slices from kindled rat and cortical slices from cortical foci in human epilepsy.[21] Thus lead to increased Ca^{2+} entry into neurons during synaptic activity[22]. Changes in metabotropic glutamate receptor act as central part in epilepsy[23].

Drugs used in Epilepsy

Drugs mainly used in treatment of epilepsy act by enhancing the GABAnergic transmission / to increase inhibition / to decrease the seizure.[24] Drugs used in epilepsy are mainly Classified on basis upon their mechanisms of action[24,25].

Table 2: Classification of antiepileptic drugs

S.NO	CLASS	Example	Uses
1.	Drugs which blockade of voltage-dependent sodium or calcium channels	carbamazepine,gabapentin, lamotrigine,oxcarbazepine, phenobarbital,phenytoin, topiramate, Valproate	Generalized, tonic-clonic and partial seizures.
2.	Drugs enhancing inhibitory events mediated by g -aminobutyric acid (GABA)	benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and Valproate	Used in all types of seizure
3.	Drugs whick blocks T-type calcium channels	Ethosuximide	Absences.
4	T-type calcium channel inhibitor	zonisamide	Generalized. tonic-clonic and partial seizures
5.	Antiepileptic drugs reduce events mediated by excitatory amino acids	Felbamate, phenobarbital, and topiramate	Generalized. tonic-clonic seizure.

Mechanisms of Action of Different Antiepileptic Drugs

Benzodiazepines (e.g. diazepam, clonazepam) and barbiturates (e.g.: phenobarbital) potentiate GABA-mediated inhibition via the increase in the affinity of inhibitory neurotransmitter to its recognition sites within the GABAA receptor complex. These drugs lead to the enhanced influx of chloride anions into the neuron and subsequent hyperpolarization.[26] Novel antiepileptic drugs (tiagabine and vigabatrin) anticonvulsant activity mainly through the GABA-ergic system. Vigabatrin, as a structural GABA analogue, binds irreversibly to GABA-transaminase which results in the inhibition of this enzyme and reduced metabolism of this inhibitory neurotransmitter. This leads to a increase in the brain GABA level.[27] Tiagabine inhibits neuronal and glial GABA uptake, leading to enhancement and prolongation of GABA synaptic events.[28] lamotrigine binds to the inactivated form of voltage-dependent sodium channels, thus limiting the sustained repetitive firing of neurons without any substantial effect upon normal synaptic activity[29]. It also reduces calcium currents via voltage

sensitive calcium channels[30]. Felbamate, gabapentin, topiramate, Tiagabine and vigabatrin show antiepileptic activity with GABA-mediated inhibition.[31] Ethosuximide or zonisamide mainly affect T-type calcium channels and felbamate, phenobarbital, and topiramate inhibit glutamate excitation[32] Gabapentin was documented to increase GABA level in brains of epileptic patients[32]. Topiramate inhibits voltage-dependent sodium and calcium currents, potentiates GABA-mediated events, blocks the AMPA/KA receptor and enhances potassium currents[33]. Felbamate enhanced GABA-dependent chloride currents in hippocampal neurons[34]. Zonisamide blocks voltage-dependent sodium channels and reduces calcium currents through T-type channels. zonisamide, enhances both, dopaminergic and serotonergic neurotransmission and inhibits glutamate-induced excitation. It also reduces the overproduction of nitric oxide and free radicals[35]. Oxcarbazepine involve blockade of voltage dependent sodium and calcium channels.[26]

Current status of antiepileptic drugs

The Food and Drug Administration (FDA) has approved several newer antiepileptic drugs: Felbamate, Gabapentin, Lacosamide, Lamotrigine, Lavetiracetam, oxcabazepine, Pregabalin, rufinamide, tiagabine, Topiramate, viagabatrin, zonnsamide for the treatment of epilepsy.[36] Another important issue in the management of epilepsy is generic substitution of innovator antiepileptic medications. The American Academy of Neurology has issued two position papers stating that there is concern with generic antiepileptic medication substitution and that physicians should specifically approve all generic substitutions.[37,38] The Italian League against epilepsy established a working group on generic products in epilepsy treatment. These generic medications offer a valuable and cost-effective choice in the management of epilepsy but that generic substitution is not recommended in patients who achieve seizure remission on an innovator product.[39]

Intranasal route

Intranasal transport is the direct transport of therapeutic agents from the nasal cavity to the brain. This is a mainly extracellular and transcellular transport, involving the olfactory and respiratory regions of the nasal cavity.[40] Pharmacological agents can bypass the BBB during this transport and enter the CNS. The BBB is normally only permeable to lipophilic molecules, with a molecular weight (Mw) less than 600 Dalton.[41] Under ideal conditions, most medication is absorbed from the nasal mucosa and reaches the cerebral cortex within 2 to 5 minutes, thus avoiding first-pass metabolism.[37] Intranasal (i.n.) drug delivery emerging as a reliable method to bypass the blood-brain barrier (BBB) and deliver a wide range of therapeutic agents including both small and large molecules. This route involves the olfactory or trigeminal nerve systems which initiate in the brain and terminate in the nasal cavity at the olfactory neuro epithelium or respiratory epithelium.[42]

Mechanism of Intra Nasal Drug Delivery to Brain

There are three mechanisms underlying the direct nose to brain drug delivery, one is intracellular transport mediated route and two extracellular transport mediated routes. The intracellular transport mediated route is a relatively slow process, taking hours for intra nasally administered substances to reach the olfactory bulb. The two extracellular transport mediated routes could underlie the rapid entrance of drug into the brain which can occur within minutes of intranasal drug administration. In the first extracellular transport based route intranasal administered substances could first cross the gap between the olfactory neurons in the olfactory epithelium which are subsequently transported in to the olfactory bulb. In second extracellular transport based route, intranasal administered substances may be transported along trigeminal nerve to bypass BBB. After reaching the olfactory bulb of trigeminal region the substances may enter in to other regions of brain by diffusion, which may also be facilitated by peri vascular pump that is driven by arterial pulsation[43].

Advantages of nasal delivery

- Nasal mucosa offers advantages to deliver drugs to brain via olfactory route thus provides rapid onset of drug action and hence faster therapeutic effect.
- Drugs are directly targeted to the CNS with intranasal delivery bypass blood brain barrier reducing systemic exposure and thus unwanted systemic side effects.
- Delivery from the nose to the CNS occurs within minutes along both the olfactory and trigeminal neural pathways via an extracellular route and does not require drug to bind to any receptor or axonal transport.
- Nasal delivery may help in reducing poor bioavailability, slow absorption, drug degradation and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver.
- Nasal route avoid the first pass metabolism effect. This delivery route also provides patient compliance, comfort and convenience.
- Formulation delivered via nasal route does not require sterile preparation
- Nasal formulation is easily and readily administered by patient or physican[44-49].

Limitation of Intranasal Route

- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.
- There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
- There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration[50].

Importance of Lipid Nanoparticle Delivery System in Epilepsy

Solid Lipid Nanoparticles

Solid lipid Nanoparticles majorly consists of lipid which is in solid form at the room temperature and surfactants for emulsification. Solid lipid Nanoparticles are generally ranging from 50-5000 nm.[42] Solid lipid Nanoparticles extend an betterment in nasal drug delivery because of their

capability to assist capsulated drug from biological or chemical environment. Nasal delivery has capability for transportation of alprazolam loaded solid lipid Nanoparticles quickly to target brain. This route avoids blood-brain barrier. The increased rate and magnitude of transfer may facilitate reduction of dose and dosing frequency. Thus allowing comfort for outdoor patient.[51]

Nanolipid carrier

Nanolipid carrier is the second generation SLN. NLC are composed of binary mixture of solid lipid and a spatially different liquid lipid as the carrier. This consists of a lipid matrix with a special nanostructure and this nanostructure improves drug loading and firmly incorporates the drug during storage. NLC accommodate the drug because of their highly unordered lipid structures.[52]NLCs of VPA were prepared by an emulsion–solvent diffusion and evaporation method followed by ultrasonication through intranasal route.[53] BBB is absent or very thin in diameter in the inter phase of brain–olfactory nerve epithelium[54]so intranasal route was chosen in the present study to bypass the BBB and promote drug distribution into the brain. In addition to this intranasal facilitate their transport across the mucosal barriers[55]. Intranasal administration allows transport of drugs to the brain circumventing BBB, thus providing a unique feature and better option to target drugs (for example lamotrigine) to the brain with quick onset of action in case of emergencies such as epilepsy.[56]

Niosome

Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle.[57]The vesicle is composed of a bi layer of non-ionic surface active agents and hence the name niosomes.[58] In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as span 60 which is usually stabilized by addition of cholesterol which gives the rigidity to the bi layer and results in less leaky niosomes[59] and small amount of anionic surfactant such as dicetyl phosphate.[60] Niosomes can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials.[61] Niosomes behave *in vivo* like liposome prolonging the circulation of entrapped drug and altering its organ distribution. Niosomes also exhibit special characteristics such as easy handling and storage. Surfactant forming niosomes are biodegradable, non-immunogenic and biocompatible.[62] Oxcarbazepine niosomes were prepared by Thin Film Hydration Technique using Rotary flash Evaporator.[63]

Liposomes

Liposomes are self-assembled structures with properties similar to biological plasma membrane: an aqueous core is surrounded by single or multiple bi layers of phospholipids. Liposomes range in diameter from approximately 50 nm to 1 μm[64]. Liposomal-entrapped curcumin also increased the latency to the onset and decreased the duration of seizures during status epilepticus in mice. Curcumin possesses poor oral bioavailability which is a major hindrance toward its pharmacological action Promising anticonvulsant effect of curcumin conclude, liposomal-entrapped curcumin possesses anticonvulsant activity against status epilepticus in mice.[65]

Table 3: List of lipid nanoparticle for the treatment of epilepsy

S.NO	Lipidic nanoparticles	Drug	size	Observation	Reference
1.	SLN	Carbamazepine	168.7 ±1.8nm	Carbamazepine loaded SLN Provide good carrier for enhancing its therapeutic effect in epilepsy.	66
		Gabapentin	159.2nm	SLN provide a beneficial delivery strategy for transportation of drug to brain and also enhancing therapeutic effect.	67
.		Diazepam	<500 nm	The incorporation of diazepam into solid lipid Nanoparticles offer advantages of rapid onset and prolonged release	68
2.	NLC	Valproic acid	154±16 nm	Valproic acid loaded NLC are good carrier for nasal delivery and provide effective protection in seizure.	69
3.	NIOSOMES	Oxcarbazepine	230-275nm	Niosomes provide effective delivery strategy for enhancing its therapeutic effect.	70
		Pregabalin		Niosomesare loaded with Pregabalin for attaining extended	71

		Valproic acid		release and longer duration of action. Niosomal loaded with valproic acid act as a promising strategy for antiepileptic drugs.	72
4.	LIPOSOMES	Amiloride hydrochloride	-	Liposomes incorporated amiloride hydrochloride is easily uptake by the CNS and also increases the antiepileptic activity of drug.	73
		Lidocaine		Liposomes has been proposed to be substantial carrier in epilepsy.	74
		Valproic acid		Surface charge on liposomes play an important role in altering antiepileptic effect of drug. Positively charged liposomes depict extended antiepileptic effect	75

CONCLUSION

Nasal delivery strategy is attractive option for treating the neurological disorder since it avoids the blood brain barrier and higher therapeutic dose reaches to brain. Lipid Nanoparticles have the greater importance in the developing field of nanotechnology with several advantages over the other formulation in term of toxicity, production, feasibility and scalability. Lipid Nanoparticles are important carrier in targeting epilepsy as they are easily uptake by CNS. This also helps in increasing the therapeutic effect of antiepileptic drugs.

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