

CHAPTER 1

INTRODUCTION

Stroke, or cerebrovascular accident, is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause. *Cerebral ischemia* is caused by a reduction in blood flow that lasts longer than several seconds. Neurologic symptoms are manifest within seconds because neurons lack glycogen, so energy failure is rapid. When blood flow is quickly restored, brain tissue can recover fully and the patient's symptoms are only transient, called as transient ischemic attack (TIA).

Other Cerebrovascular diseases include some of most common and devastating disorders like hemorrhagic stroke, and cerebrovascular anomalies such as intracranial aneurysms and arteriovenous malformations (AVMs).

Ischemic Stroke is the third leading cause of death and the main cause of long-term disability in western societies (1). It has been estimated that worldwide approximately 5.7 million people die from acute ischemic stroke per annum. Risk of Recurrent stroke ranges from 5% to 20% after cerebrovascular diseases per year (2) and the lifetime risk of stroke is between 8%-10% (3). The incidence of cerebrovascular diseases increases with age, and the number of strokes is projected to increase as the elderly population grows, with a doubling in stroke deaths in the United States by 2030.

The pathophysiological mechanisms of cerebral stroke includes energy failure, free radical generation, elevation of intracellular ca^{+2} level, excitotoxicity, inflammation and apoptosis to cell death. Pathophysiology of the cerebral stroke involves complex cascade events which lead to cellular death via necrotic pathway and apoptotic pathway; In first mechanism, due to the energy failure or loss, rapidly breakdown of cytoskeletal occurs. While in apoptotic pathway, programmed death of cells occurs. Depletion of glucose leads to failure of mitochondria to produce ATP. As a consequence of lack of ATP production, membrane function stops and neurons becomes depolarise and intracellular level of calcium increases. Depolarization of cells further cause the release of excitatory neurotransmitter glutamate in the synaptic terminals causing excitotoxicity of the cells. Free radical species generated by dysfunctioning of mitochondria and lipid degradation of membrane causes catalytic degradation of membranes and damage other vital cellular functions. Oxygen radicals serve as important signalling molecules that trigger inflammation and apoptosis.

different cerebral conditions like ischemic stroke (4, 5, 6). Agents that can produce neuroprotection by primarily targeting the cerebral vasculature includes agents like anti-thrombotics and antiplatelets that can prevent clot formation and agents like thrombolytics that can break down existing clots considered as indirect neuroprotectants which are mentioned above, while agents that directly act upon the neuron itself are considered direct neuroprotectants. Neuronal death occurs by the cerebral stroke cascade events. Within these cascade events, many molecular targets can be modulated pharmacologically to produce neuroprotection (7). Neuroprotectants that targets cascade events includes free radical production, intracellular Ca^{+2} influx, glutamate release, excitotoxicity, nitric oxide production, inflammation and apoptosis (6). Even though, there are many numbers of clinical trials; neuroprotective agents yet have not been proven to be beneficial in humans. Agents which are tested in phase II and III trials includes calcium channel blockers, free radicals scavengers and antioxidants, GABA antagonists, AMPA antagonists, competitive and non-competitive NMDA antagonists, inflammation blockers, adhesion inhibitors, nitric oxide inhibitors, opioid antagonists, serotonin antagonists, Na^{+} and K^{+} channel blockers etc.

Nicergoline is an ergoline derivative which is used to treat cognitive deficits, dizziness (8, 9) and its having positive effects on psychomotor performance, concentration and neurophysiological parameters. Nicergoline increases the cerebral blood flow and monoamine turnover and affects cholinergic function in the aged rat brain (10). It was reported that nicergoline has a protective effect against ischemic brain damage in ischemic brain models (11, 12). One study demonstrated that nicergoline suppressed the production of pro-inflammatory cytokines and superoxide anion generation by activated microglia and astrocytes. Through the effect on glutamate transporters (13) nicergoline reduces the extracellular glutamate and plays a role as a neuroprotective. Further, nicergoline by inducing TGF- β and glial-derived neurotrophic factor protects cultured neurons against β -amyloid toxicity.

Recently, there are many types of drug delivery carriers are being developed or in developing stage with an objective to improve drug bioavailability, to reduce toxicity and side effects, to prevent degradation or loss upon administration. These drug delivery carriers include liposomes, nanoparticles, microcapsules, microemulsions, micelles etc. Micelles as a drug carrier have gained more attention in recent years, among those delivery systems. Bioavailability of poorly soluble drugs can be improved by incorporating drug into core-shell

structure of micelles. Due to smaller particle size of micelle carriers, they can accumulate spontaneously in damaged vasculature via Enhanced Permeability and Retention(EPR) effect.

Micelles spontaneously form when the concentration of the amphiphile unimers is higher than a critical concentration (CMC). Below the CMC amphiphilic molecules are absorbed at the air-water interface. At the CMC the amphiphile becomes saturated at this interface and in the bulk solvent, and it becomes entropically favourable for micelles to form to minimize the free energy of the system.

Polymeric micelles consist of a core and shell structure in which the inner core is the hydrophobic part of the block copolymer, whereas the outer shell or corona of the hydrophilic block of the copolymer. Core structure encapsulates the poorly water-soluble drug while shell structure protects the drug from the aqueous environment and stabilizes the micelles against in vivo recognition by RES.

Polymeric micelles increase the solubility of poorly soluble drugs, having physicochemical properties for tumor targeting by passive targeting via EPR effect. Micelle drug carriers can be targeted at particular specific site by ligand coupling. Various ligands include monoclonal antibodies-mAbs (Immunomicelles), folate residues, peptides, luteinizing hormone-releasing hormone, epidermal growth factor (EGF), α 2-glycoprotein, transferrin, sugars etc. Outer surface functionalization of polymeric micelles can modify the physicochemical and biological properties of micelles systems for receptor mediated Drug delivery.

Recently, nasal route as drug delivery gained much more attention because it offers several advantages like bypass of first pass metabolism, rapid absorption and preferentially brain delivery for treatment of CNS disorders. Various dosage forms to deliver drug via intranasally includes nasal drops, nasal spray, nanoparticles, microemulsions, liposomes, nasal powders etc.

References

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