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Nanocapsulated Antioxidants in Combating Mitochondrial Generated Oxidative Stress in Cerebral Ischemia-Reperfusion Injury

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Short Communication

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ABSTRACT

Toxic reactive oxidative species (ROS) evoked by the induction of oxidative stress in the episode of cerebral ischemia reperfusion (CIR) play the key role in neurodegeneration. As it is the prime source point of ROS, neuronal mitochondria, the cellular energy metabolic centre suffer severe damage in response to cerebral ischemic oxidative thrust. In aging, CIR accelerates the process of mitochondrial dysfunction. Increasing evidence suggests that oxidative stress mediated defects in mitochondrial energy production may be involved in numerous age related neurodegenerative disorders. Impairment of mitochondrial function causes generation of free radicals e.g., O2-, •OH. Normally free radicals are generated as by-products of oxidative metabolism. An increase in super oxide radical generation can have direct as well as indirect damaging consequences on the metabolism of neuron. From therapeutic point, the application of chemical antioxidants is almost ineffective as the blood-brain barrier (BBB) limits the passage of molecules from the circulation into the cerebral region. Nanoencapsulation technology has proven benefits for the ability to cross the BBB as well as their nature to increase cellular drug concentration. Particle size and size distribution play the determining role in drug delivery systems. The NP size less than 100 nm particles experiences reduced hepatic filtration and takes less time to reach the brain, the target organ in my present communication

INTRODUCTION

Ageing is one of the most significant risk factor for degenerative neurological disorders. Experimental evidence indicates that oxygen free radical attack is a potential threat on neuronal cell survival in age related cerebral diseases including cerebral ischemia-reperfusion. Diseases of brain from acute one such as stroke to chronic one like senile dementia of Alzheimer type cause a major percentage of death and debility in our ageing society and generation of ROS by mitochondria is a common feature in most of those cerebral diseases. Over the past few decades, free radical, the highly reactive and thereby destructive molecule has got the importance as a potential research component for its key role in aging process. In initial phase of free radical mediated neurodegenerative diseases, neuronal cells trigger their effective protection mechanism to counter the oxidative damage. Cerebral ischemia and reperfusion injury is a particularly fascinating example of free radical mediated neurodegenerative disease. When brain is deprived of its blood supply (ischemia), its injury is not only just by the temporary loss of oxygen and energy supply, but also by the reactive oxygen species that are generated by reactions with the oxygen that is reintroduced during reperfusion. CIR induced ROS causes oxidative damage to brain bio-membrane, proteins, lipids and DNA leading to brain dysfunction and neuronal cell death [1]. Data in our lab [2] showed that CIR injury caused extensive lipid peroxidation in the experimental rat brains. Peroxidation of lipids can disrupt membrane integrity, causing alteration in fluidity and permeability, inhibition of metabolic processes, and imbalance of ion transport regulation [3].

Pretreatment with Nano encapsulated antioxidant (resveratrol) effectively reduces the CIR induced membrane lipid peroxidation, brings the endogenous antioxidative enzyme activities close to their normal levels and maintains the normal intracellular GSH pool. As the cellular abnormalities after CIR are mainly due to the produced ROS, hence it may be said that the Nano compounds directly scavenge the generated ROS to prevent the cells from oxidative injury. In contrast, free compounds treatment hardly shows any effect in preventing the CIR injury of the experimental animals. Studies on mitochondrial ultra-

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structures have proven damaging effects due to CIR injury [4]. It has been observed from studies in our lab by Ghosh [5] that CIR injury strongly affected the mitochondria of the brain cells. Significant drop in mitochondrial membrane micro viscosity is observed and it indicates a distortion of polar/a polar ratio of mitochondrial membrane. Nano compounds treatment prior to CIR insult in rats can successfully decrease the mitochondrial ROS generation and maintains the mitochondrial membrane fluidity whereas free compounds could not impart any significant improvement to the brain cells as was evident from the studies. In this report, same effect has been observed in total fraction of cells i.e., Nano compounds not free compounds scavenge ROS. The value of lipid peroxidation is diminished increasing the value of micro viscosity of total fraction as in **Tables 1 and 2 (Figure 1)**.

CIR caused the release of cytochrome-c from mitochondria into the cytosol with a positive correlation of ROS generation and leading to cellular apoptosis. This data was further supported by the results of tissue histology where significant amount of neuronal cell loss was noticed [6]. Detection of apoptotic cells further confirmed those observations. The levels of COX-2 and iNOS also increased due to ischemic insult. Significant protection against oxidative attack was imparted by the administration of Nano compounds before the induction of CIR. Levels of cytochrome c, COX-2 and iNOS significantly decreased in cytosolic part, leading to an excellent protection against neuronal cellular apoptosis.

Table 1. Effects of ischemia-reperfusion on ROS generation and lipid peroxidation in young rat brain total and cytosolic fraction and their regulation by free and Nano compounds. Results are expressed as mean ± SE.

GROUP	ROS	Lipid Peroxidation (µM)
Normal (Total fraction)	100 ± 8.49	5.405 ± 0.11
Ischemia (Total fraction)	249 ± 13.54	6.675 ± 0.35
Drug (Total fraction)	230 ± 16.49	6.487 ± 0.33
Nano (Total fraction)	121 ± 11.46	5.433 ± 0.89
Normal (Cytosolic)	100 ± 6.98	6.743 ± 1.13
Ischemia (Cytosolic)	223 ± 9.84	8.284 ± 0.94
Drug (Cytosolic)	211 ± 11.47	8.062 ± 0.99
Nano (Cytosolic)	115 ± 12.95	6.967 ± 1.03

Table 2. Effects of ischemia-reperfusion on young rat brain mitochondrial membrane microviscosity and its regulation by free and Nano vesiculated compounds.

Group	Microviscosity
Normal (Total)	0.89 ± 0.04
Ischemia (Total)	0.34 ± 0.01
Drug (Total)	0.46 ± 0.01
Nano (Total)	0.78 ± 0.07

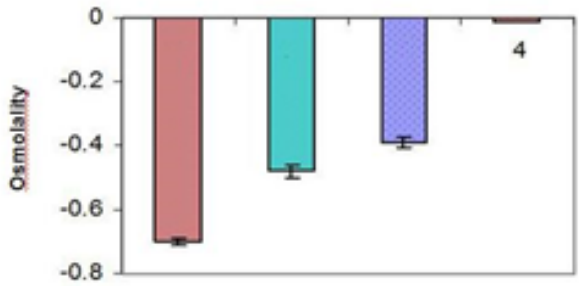

Figure 1. Osmolality difference (osmoles/cc) among control, treated groups, CIR and drug-treated groups. Values are mean+SD.

DISCUSSION

Pretreatment with free compounds could not reverse the situation as evident from the intracellular malondialdehyde values. However, Nano compounds reduce the CIR induced lipid peroxidation to the near normal values. Vesiculated compounds with a size of 100 nm are effective even for a longer time period. Cerebral ischemia resulted in a significant increase in brain cell edema. This edema development is a measure of uncontrolled entry of plasma water in the cells and a loss of BBB integrity. Vesiculated compounds also decreased edema development in brain cell. Bilateral common carotid artery occlusion in rat for 30 min followed by 6 hr. reperfusion cause a massive inhibition of MMPs [7] in rat brain. Liposomal compounds are very effective (data not shown) in comparison to free compounds though Nano vesiculated formulation is more active due to non-biodegradability. It has been observed that cellular damage resulting from the oxidation of biomolecules play significant roles in neuronal associated age related disorder i.e., cerebral ischemia. In this study attempts would be made to introduce vesiculated antioxidants namely Nano vesiculated forms to brain to combat cerebral ischemia-reperfusion induced oxidative injury using *in vivo* cerebral ischemia and re-perfused rat model.

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CONCLUSION

This present communication opens a new avenue that Nano encapsulated technology demonstrates a new direction in the treatment of cerebral stroke. Thus, herbal antioxidants in Nano vesiculated drug delivery system may be a potential protective approach in the treatment of cerebral stroke.

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