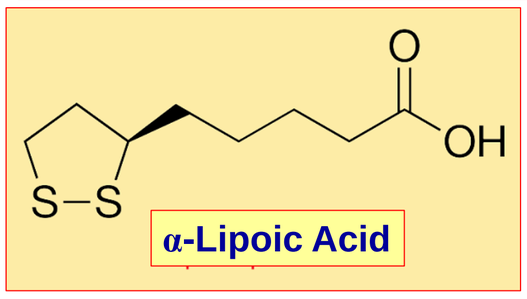
IECBS 2024 Conference
The 4th International Electronic Conference on Brain Sciences
23–25 October 2024 | Online
MDPI

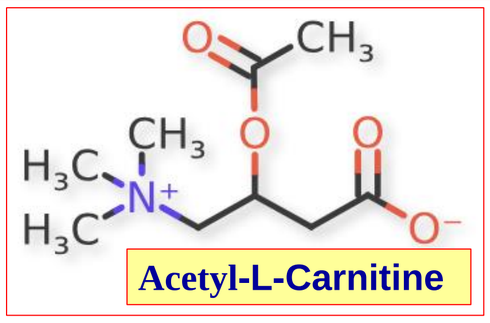
Neuroprotective Effects of Selected Natural Ergogenic Antioxidant Poly(ADP-Ribose)Polymerase-1 Inhibitors Against Experimentally Induced Alzheimer's Disease in Aged Rats

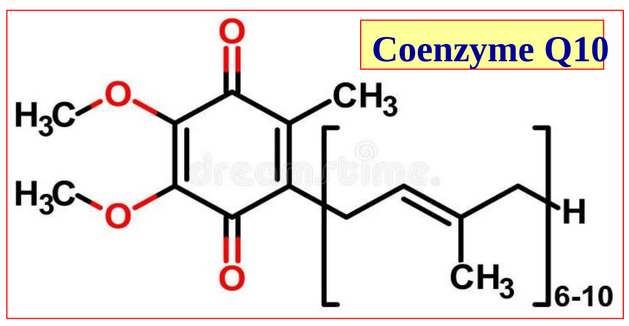
Kumar Ponnusamy[1], Siddarth Srigokul Kumar[2], Sripriyanka Kumar[3], Siva Thirisangu[4], Samith Ahmed[5], Samira Abdul Wajid[6], Ajit Kumar Rampure[7] & Parvathi Rampure[8]
Aureus University School of Medicine (AUSOM), Oranjestad, Aruba[1,4-8]
School of Medicine, Pondicherry Institute of Medical Sciences, Pondicherry (PIMS), India[2]
School of Medicine, Indira Gandhi Medical College & Research Institute, Pondicherry, India[3]

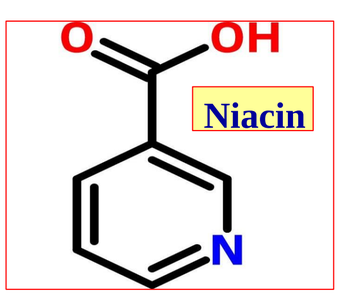
INTRODUCTION & AIM

Oxidative stress (OS), inflammation, and ultimate irreversible membrane molecular mitochondrial damages and genome instabilities are implicated in aging and age-related progressive neurodegenerative diseases (NDDs), such as Parkinsonism, Senile Dementia and Alzheimer's Disease (AD). α-Lipoic acid, acetyl-L-carnitine, coenzyme-Q10, and niacin are iron-chelating antioxidant ergogenic-aids which play a pivotal role and exert cytoprotective effects against innumerable neurodegenerative diseases (NDDs). The ICV injection of streptozotocin (STZ) leads to neurodegeneration. This present study is used to estimate the neuroprotective effect of selected natural poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors on the biomarkers of OS and genome instability, inflammation, and DNA repair enzymes in STZ-induced neurotoxicity.









METHOD

Male aged albino rats (24 months old, 350 gm body wt) were pretreated with α-lipoic acid and/or, acetyl-L-carnitine, coenzyme-Q10 and niacin (started 3 days prior to STZ) (100mg/kg b.wt, i.p for 21 days), followed by bilateral i.c.v injection with the DNA-destabilizing genotoxin STZ (100mg/kg b.wt). At the end of the 21 days, the hippocampus was dissected-out, and relevant biochemical parameters were estimated in brain and serum samples.

RESULTS & DISCUSSION

The combined application of ergogenic antioxidants mitigated the toxic onslaught of SZN-induced neurotoxicity and exerted neuroprotection by significantly reducing MDA, 8-OHdG, AChE activity, IL-6, TNF-α, XO, NOS, the augmentation of antioxidants, ATP, DNA and NTs, and the modulation of PARP-1. PARP-1 expression was found to increase exponentially with the severity of OS and was found to decrease significantly with decreased OS.

Table 1. Effect of Selected Natural Ergogenic Antioxidant Poly(ADP-Ribose)Polymerase-1 Inhibitors Against Streptozotocin (STZ) Induced Neurotoxicity in Aged Rats

No	Parameters	Group-1 Control	Group-2 STZ	Group-3 STZ + ALA	Group-4 STZ + ALC	Group-5 STZ + CoQ10	Group-6 STZ + Niacin	Group-7 STZ + ALA + ALC + CoQ 10+ Niacin
1	MDA (nmol/mg of protein)	3.19±0.83	4.58±0.04	3.82±0.06	3.76±0.09	3.89±0.06	3.76±0.27	3.47±0.28†
2	8-OHdG (fmol/µg DNA)	18±1.14	39±1.32†	32±1.34†	29.5±1.28*	27.4±1.28†	26.80±1.30†	23.80±1.30†
3	AChE activity (µm of substratehydrolyzed/g/min)	1.28±0.12	1.05±0.12†	1.32±0.14†	1.36±0.14*	1.39±0.15†	1.46±0.15†	1.83±0.15†
4	IL-6 (pg/mg)	28±1.8	42±2.33†	39±2.35†	34±2.85*	35.5±3.16#	34±2.65†	32±2.65†
5	TNF-α (pg/ml)	243±14.30	336±19†	328±20†	286±17*	274±18#	271±20†	267±19†
6	XO (µM/mg protein)	3.23±0.03	4.97±0.04†	4.88±0.05†	3.61±0.07*	3.71±0.06#	3.65±0.03	3.23±0.03
7	NOS (nmol of Nox/g wet tissue/hr)	123±8.5	247±9.3†	243±9.2†	232±10.8*	238±11.6†	234±9.60†	229±9.60†
8	ATP (mM/kg wet tissue wt)	3.35±0.23	2.56.±0.19†	2.89±0.18†	3.24±0.23*	3.20±0.27†	3.45±0.24†	3.52±0.26†
9	DNA (mg of DNA/gm tissue)	1.38±0.12	1.18±0.17†	1.29±0.19†	1.26±0.15*	1.29±0.17#	1.87±0.13†	1.93±0.15†
10	Dopamine (ng/g tissue)	3360±116	2376±122†	2870±132†	3126±108*	3228±132†	3239±137†	3286±137†
11	NE (ng/g tissue)	342±18	267±17†	317±19†	372±14*	380±15†	386±16†	397±18†
12	PARP-1 (Units/mg protein)	6.74±0.34	9.58±0.37†	8.78±0.43†	8.23±0.0.3*	7.85±0.28†	7.14±0.29†	5.84±0.39†

Values are expressed as mean± SD for 6 animals in each group. On comparing groups, Group 2 with Group-1 ; Groups-3-6 with Group-2; Group-7 compared with Group-2. *P<0.05, #P< 0.01, †P<0.001.

CONCLUSION

The combined application of ergogenic antioxidant poly(ADP-ribose) polymerase-1 inhibitors such as α-Lipoic acid and/or, Acetyl-L-carnitine, Coenzyme-Q10, Niacin, will be effective in the treatment and/or management of progressive NDDS such as Alzheimer's Disease (AD).

Key Words: Alzheimer's disease, Oxidative stress, Neurodegeneration, Dementia, Antioxidant, Ergogenic aids, Mitochondrial medicines, Iron-chelating antioxidants, ATP, Neuroprotection.

FUTURE WORK

The potential of PARP-inhibitor (PARP-i) therapy in a variety of neurodegenerative diseases has been highlighted by the significant numbers of preclinical studies and clinical trials, demonstrating their superior efficacy over traditional chemotherapies in such as dementia. However, although the clinical relevance of PARP-i is clear, the underlying mechanisms of PARP-i activity remain elusive; therefore, limiting our understanding of potential targets for PARP-i neurodegenerative biomarkers and pathways of genome stability. Further studies of the mechanism of action of natural PARP-i are required, along with the validation and approval of additional biomarkers to ensure that PARP-i therapy is utilized to provide maximal AD patient benefit.

REFERENCES

Dapinder Kaur, Tapan Behl, Aayush Sehgal. Decrypting the potential role of α-lipoic acid in Alzheimer's disease. Life Sciences,Vol 284, 1 Nov 2021, 119899-913. Acetyl-L-Carnitine in Dementia and Other Cognitive Disorders: A Critical Update. Nutrients 2020, 12, 1389-11.

Zden ek Fišar and Jana Hroudová. CoQ10 and Mitochondrial Dysfunction in Alzheimer's Disease. Antioxidants, Feb 2024, 13, 191-22.

Emily Wuerch, Gloria Roldan Urgoiti, V. Wee Yong. The Promise of Niacin in Neurology. Neurotherapeutics (2023) 20:1037-54.

V. Maluchenko, Alexey V. Feofanov, and Vasily M.Studitsky. PARP-1-Associated Pathological Processes: Inhibition by Natural Polyphenols Natalya Int. J. Mol. Sci.2021,22,11441-59.