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PhD Dissertation Defense

Entitled

THE ROLE OF HUMAN A7-NICOTINIC ACETYLCHOLINE RECEPTORS IN MEDIATING NEUROPROTECTIVE ACTION OF CURCUMIN

by

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Abstract:

Curcumin is a polyphenolic compound isolated from the rhizomes of Curcuma longa (turmeric). Curcumin has been demonstrated to have antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties. Moreover, it has been shown to exhibit beneficial effects in treatment of several neurodegenerative diseases such as Alzheimer and Parkinson's diseases, and psychosis. However, molecular and cellular targets mediating the pharmacological actions of curcumin remain largely unknown. In this study, the effects of curcumin application on the functional properties of nicotinic acetylcholine receptor, a prototype for ligand gated ion channels were investigated. First, using two-electrode voltage clamp technique, the results showed that curcumin application caused a significant potentiation of the action of human α7-nicotinic acetylcholine receptors (α7-nAChR) expressed in *Xenopus* oocytes. Importantly, curcumin was found ineffective on other nicotinic receptor subunit combinations and other members of ligand-gated ion channels. Curcumin significantly decreased desensitization of the receptor suggesting that it acts as a type II PAM. High affinity binding site for curcumin was also verified by our molecular docking study. In the second part of this study, the neuroprotective effects of curcumin in an animal model of Parkinson's disease was investigated. Stereotaxic micro-neurosurgery was successfully established (first time in our university) and used to induce the toxin based (6-hydroxydopamine; 6-OHDA) animal model of Parkinson's disease. This was followed by testing the behavior of the animals, tissue collection, immunohistochemistry, and stereological data analysis. In-vivo results suggested that curcumin has potential neuroprotective properties against 6-OHDA animal model of Parkinson's disease. Systemic administration of curcumin alleviated 6-OHDA-induced motor abnormalities and protected against substantia nigra pars compacta dopaminergic neuronal loss, through an α7-nAChRs-mediated mechanism. The protective effects of curcumin were reversed by administration of the α7-nAChR-selective antagonist methyllycaconitine (MLA). In summary, the results of this study suggest that α7-nAChR-mediated activation is an important mechanism underlying the neuroprotective effects of curcumin in an animal model of Parkinson's disease.

Keywords: Curcumin - α7-nAChR - *Xenopus* oocytes - Parkinson's disease - 6-OHDA - neuroprotection.