

ABSTRACT

The Interaction between Long Term Potentiation and Excitotoxins

Farid Youssef

This thesis sought to examine whether or not long term potentiation (LTP) might alter the responsiveness of neurons to a number of glutamate agonists in the rat hippocampal slice. LTP is dependent on the activation of NMDA and AMPA receptors and such an effect is not unlikely considering previous research has suggested the existence of various types of interaction between glutamate receptors.

Initial studies made use of extracellular recordings of population spike potentials (PSPs) and field excitatory post-synaptic potentials (fEPSPs) while the agonists were allowed to superfuse the slice. This work demonstrated that LTP reduced the sensitivity of the hippocampal neurons to all agonists tested when PSPs were recorded. Subsequent micro-iontophoretic studies confirmed this and demonstrated that the effect occurred at both somatic and dendritic receptor populations. Desensitization studies designed to serve as controls for these

experiments suggested the existence of separate sub-populations of NMDA and quinolinic acid receptors within the hippocampus.

In an attempt to elucidate the mechanism responsible for this phenomenon the experiments were repeated in the presence of nitric oxide synthase inhibitors and also inhibitors of AMPA receptor desensitization. The results highlighted that NOS inhibitors abolished the effect of LTP upon NMDA receptor sensitivity, but not AMPA, though cyclothiazide prevented the effect of LTP upon AMPA receptor sensitivity. I therefore propose a model that extends the ranges of retrograde messengers beyond the pre-synaptic neuron and spreads the signal elicited by tetanic stimulation to a number of other nearby but extra-synaptic receptors.

Excessive activation of glutamate receptors is known to lead to excitotoxic cell death. The work was therefore extended and examined the effect of LTP on different pathological models of hypoxia-ischemia. LTP was found to protect the neurons from injury. Further work now needs to be undertaken to ascertain the exact mechanism behind this phenomenon and its usefulness in determining possible therapeutic interventions in CNS disease processes.

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Keywords: LTP; NMDA; desensitization; neuronal sensitivity; excitotoxicity.