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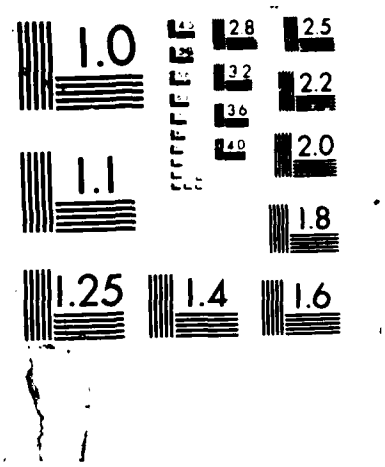
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16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB GR.	Synapse; plasticity; reactivity; phosphorylation; protein kinase C; protein F1; fatty acids

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

This research is focussed on the role of molecular switches in brain which regulate synaptic reactivity. We have identified a 47,000 mol wt phosphoprotein and its kinase (c) which play a pivotal role in this regulation. We have enhanced communication among nerve cells studied electrophysiologically by activation of this kinase. In the proposed research we specifically manipulate this brain phosphoprotein with novel kinase activating agents. In a new initiative, both the kinase and the F1 substrate will be studied with the goal of enhancing synaptic reactivity by regulating the activity of proteins that play a pivotal role in this process.

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Annual Technical/Scientific Report

1. Project Period The project period includes October 1, 1986 to September 30, 1987. The present report is being filed in August, 1987.

2. Summary

The regulation of synaptic reactivity by protein kinase C and its substrate proteins has been studied using the long-term potentiation paradigm (LTP). In the past year we have studied the effects of protein kinase C activators and inhibitors on durability of synaptic reactivity. The main conclusion to be drawn is that protein kinase C is necessary but not sufficient for the enhanced durability. In combination with a neural signal, however, PKC demonstrates a profound synergism. Synergism is also observed in the analysis of metal ion regulation of protein kinase C activity. Calcium and zinc interact in their effect on the enzyme in a bidirectional manner (see below).

3. Statement of Work

The research objectives during this period were to:

a. Study effects of protein kinase C inhibitors

b. Study activators of PKC in the synaptic zone

c. Study metal ion regulation of PKC

4. Status of Research

Significant accomplishments made during this period were:

a. Effect of inhibitors

We used three separate inhibitors of protein kinase C activity,

polymyxin B, mellitin and H-7, each with a different mechanism of action. Application was made by micro-pressure ejection into the molecular layer of the dentate gyrus before or after LTP. The major result of this study was that inhibitors had no effect on the initiation of LTP but completely eliminated the enhanced response 10-15 min after its initiation. This provides strong support for our view that PKC plays a critical role in the maintenance but not the initiation of LTP.

b. Study of PKC activators (PDBu and oleate)

A crucial question in the analysis of the role of PKC in synaptic reactivity is the site of action of the compound. Indirect evidence suggested a synaptic site since PKC is found in high concentration there. To assess this view directly we compared application dosages required to facilitate synaptic reactivity duration in the dentate hilus, a nearby site, and the molecular layer of the dentate, 100 micra from the granule cells, precisely the point where perforant path terminals synapse. We have found that only 10-16% of the dosage is required when the application, iontophoretic or micro-pressure, is made at the synaptic zone. This provides strong support for the synaptic site of action of these protein kinase C activators.

c. Metal ion regulation of protein kinase C activity

Recent evidence describing the primary structure of protein kinase C by several laboratories indicates several different motifs: ATP-binding, Ca-binding, kinase domain, zinc "fingers". This suggested the possibility that both zinc as well as calcium might regulate protein kinase C activity.

Since we have recently discovered that protein kinase C can be activated in the absence of calcium it was now feasible to sstudy the effects of zinc both in the presence and the absence of calcium. A novel mechanism for regulating protein kinase C activity was discovered in which zinc ions, found in highest concentration in the hippocampus, enhance protein kinase C activity at low calcium levels. At higher levels of calcium, zinc inhibits. We propose a model of protein kinase C with a low and high calcium affinity binding sites and a distinct zinc binding site.

5. Articles published, accepted for publication and submitted.

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correlated with persistence of long-term potentiation: A quantiative analysis of two-dimensional gels. Submitted.

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transplantation. In: Progress in Brain Research (J. Slarek and D. Gash, Eds.), Vol. 82, 1988, in press.

6. Personnel

Name	Title	Dates of Service	% Effort
A. Routtenberg	Professor/PI	9/83-present	25%
S. Chan	Res. Neurobiologist	2/84-present	25%
K. Murakami	Res. Neurobiologist	4/84-present**	25%
P. Colley	Grad. Res. Asst.	7/83-present	50%
D. Linden	Grad. Res. Asst.	9/84-present	50%
D. Lovinger	Grad. Res. Asst.	7/83-present*	50%
R. Nelson	Grad. Res. Asst.	7/83-present*	50%
F. Sheu	Grad. Res. Asst.	9/85-present	50%
K. Wong	Grad. Res. Asst.	4/86-present	50%

* - Ph.D. awarded 6/87

** - Assistant Professor, University of Buffalo, September, 1987.

7. Coupling Activities

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