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RISK FACTORS, AGING, AND SIGNAL TRANSDUCTION: SPECIAL REFERENCE TO METALS AND INOSITOL PHOSPHOLIPID METABOLISM

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ABSTRACT

The effects of several metal ions on the metabolism of (poly-) phosphoinositides in rat brain membranes were studied. It appeared that divalent as well as trivalent ions exerted differential effects on the phosphorylation of the phosphoinositides, suggesting a role of this polyphosphoinositide (pPI) system in the healthy functioning of the brain, in neurological disorders related to age, and in brain dysfunctions due to exposure to neurotoxic metals.

INTRODUCTION

The pPI metabolism is an intermediate system involved in the process of trans membrane neuronal signal transduction. Therefore, the study of the pPI metabolism may lead to a better understanding of processes, such as ageing, that affect signal transduction. Receptor stimulation leads to phospholipase C (PLC) activation subsequently cleaving pPI into the well known second messengers diacylglycerol (DAG) and inositolphosphates. On the other hand,the pPIs are interconverted into each other by membrane-bound, specific kinases and phosphomonoesterases. DAG is rapidly phosphorylated into phosphatidic acid (PA) by cytosolic DAG-kinase, after which in the endoplasmic reticulum pPI is reconstituted from PA-CMP and inositol. In our laboratory the effects of risk factors - known to be likely involved in processes such as mental retardation and/or neuronal degradation- on this pPI metabolism are studied in relation to ageing. Several metal ions play an essential role as "micro-" and "macro-minerals" (present in the mammalian brain in μmolar and mmolar concentrations respectively) in the living organism. More specifically, Mg^{++} is essential for the kinases and monoesterases involved in the pPI metabolism, Ca^{++} for PLC activity, and Mn^{++} and Mg^{++} are essential for the transferases. Several metal ions not belonging to these essential elements are known for their (neuro-)toxic effects: These include Cd^{++}, Hg^{++}, Pb^{++}, and Al^{+++}. The present study reports on the differential effects of several metal ions on the PI metabolism. Especially those metals receive attention which are implicated in aging processes and neurodegenerative diseases, such as for instance Zn^{++} and Alu^{+++}.

EXPERIMENTAL PROCEDURE

Following the approach of Jolles et al. (1980), a lysed crude mitochondrial/synaptosomal fraction from rat brain homogenate was prepared and phosphorylation started by the addition of ATP, using radiolabeled ATP. After termination of the reaction and subsequent lipid extraction, thin layer chromatography revealed phosphate incorporation in PI-phosphate (PIP), PI-bis phosphate (PIP2) and PA.

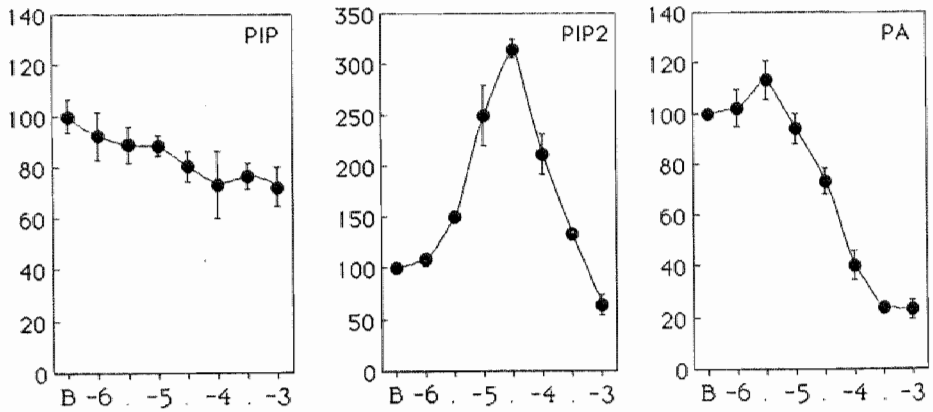

Fig. 1 Effect of Ni^{++} on inositollipid phosphorylation. Abscissa: log concentration of cation during incubation, B: no cation present. Ordinate: phosphate incorporation as percentage of control level.

RESULTS

Incubation of the homogenate in the presence of monovalent metal ions (K^{+}, Li^{+} in a dose range of 1 μM to 1 mM) prior to ATP addition had no effect (data not shown), whereas (1 μM to 1 mM) Mn^{++}, Co^{++}, Ni^{++}, Cu^{++}, Zn^{++} (in Fig. 1, the dose response curve of Ni^{++} is given), and Cd^{++}, Hg^{++}, Pb^{++} (Fig. 2, Pb^{++}) exerted differential effects on PI metabolism. Al^{+++} and Au^{+++} inhibited PIP, PIP2 and PA formation dose-dependently (Fig. 3, Al^{+++}).

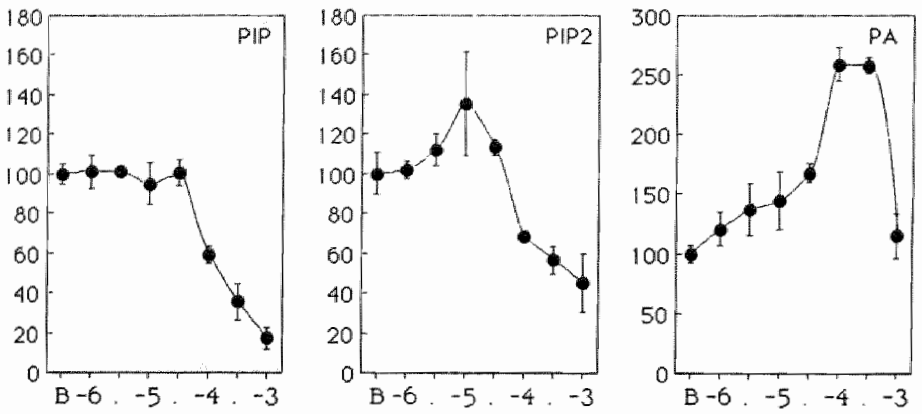

Fig. 2 Effect of Pb^{++} on inositollipid phosphorylation. For legends, see Fig.1.

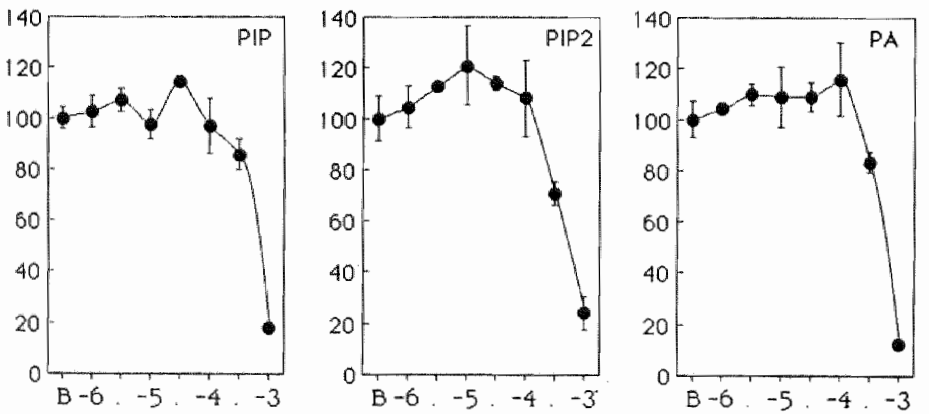

Fig. 3 Effect of Al^{+++} on inositollipid phosphorylation. For legends,see Fig.1.

DISCUSSION

At which level may these ions interfere with pPI metabolism? Cations may form complexes with ATP, selectively interact with monoesterases, PLC, or with one or more of the involved kinases, interfere with transferase activity. We have good indications that in our assay system no PLC activity is present under basal conditions. This is the more likely since no Ca^{++} is present during the incubation. Pb^{++} stimulates PA, and PIP and PIP2 are inhibited Fig. 4), this could point to a stimulation of PLC activity. This is in agreement with findings reported in literature that Pb^{++} can "imitate" Ca^{++} at the biochemical level. The chemical parameters of a certain cation -such as ion radius, coordination number, or character of binding with chelators- can not simply explain the differential effects we found with most metal ions. As far as we tested, metal ions can only be grouped on charge with respect to the effects found: Monovalent ions are not effective, bivalent ions exert differential effects, and trivalent ions only inhibited phosphate incorporation in PIP, PIP2, an PA. Further research will be directed to uncover possible mechanisms. The possibility that metal ions are involved in neurodegenerative processes such as Alzheimer disease is recovering increasingly interest, whereas a causal relation to certain syndromes is amply documented (eg Aluminum encephalopathy). Based upon the results presented here, follow-up research is now being performed with the same ions in brains of old rats and of Alzheimer brain material.

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