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# Therapeutic and pathological signals of cell membranes

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**I. Cyclic glycerophosphates – Novel signaling molecules**
These simple (though overlooked) molecules were found to be formed as intermediates in the enzymic cleavage of phosphatidyl glycerol. The structural analogy between 1,3 cGP and cyclic AMP prompted us to investigate the signaling potential of 1,3 cGP, 1,2 cGP and their deoxy analogues. The linear forms of 1,3 cGP and 1,2 cGP, i.e. a-glycerophosphate and b-glycerophosphate served as control compounds.

**The results of 6 years of intensive investigation can be summarized as follows:**

1. 1,3 and 1,2 cGP and their deoxy analogues, at the micromolar range, can induce intracellular tyrosine phosphorylation of a series of signaling proteins.

2. Breast cancer cells can be differentiated to an estrogen receptor/progesterone receptor positive state by these compounds.

3. Similarly, these compounds can induce neuronal-like differentiation of PC12 cells (Fig. 1).

4. In collaboration with the group of Dr. Gal Yadid in Bar-Ilan University, studies on Parkinsonian rats indicated a significant therapeutic potential for Parkinson's disease of these compounds.

**II. Pressure induced tumor vaccines**
When tumor cells are subjected to hydrostatic pressure (P) in the presence of a specially designed membrane crosslinker (CL) they become highly immunogenic due to a substantial increase in the surface presentation of MHC components and antigen presenting stress proteins. We have lately shown that subsequent reduction of surface protein disulfides with N-acetyl-L-cysteine (NAC) further augments the immunogenic potential of PCL-modified tumor cells both *in vitro* and *in vivo*. Immunotherapy with PCL+NAC modified 3LL-D122 Lewis lung carcinoma cells plus intravenous delivery of NAC in mice bearing established lung metastases provoked the most effective anti-tumor response capable of eradicating the metastatic nodules as demonstrated by restoration of normal lung weight and histology. In addition, immunization with PCL+NAC modified tumor cells gave rise to a strong delayed type hypersensitivity (DTH) recall response against parental D122 cells. We propose that this novel two-prong strategy, based on local immunization with autologous PCL+NAC modified tumor cells and systemic boosting with NAC, could provide a practical, effective immunotherapeutic regimen for the treatment of human cancer. Clinical studies with this novel and innocuous regimen are being planned.

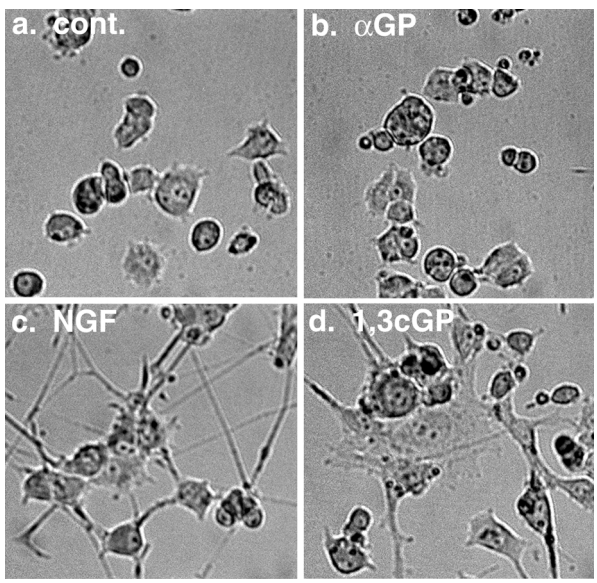


***Fig. 1*** *Morphology of PC12 cells after 8 days in culture in the presence of 50 ng/ml NGF (c) and 0.5 mM 1,3 cGP (d). Control cultures were grown in the presence of 0.5 mM aGP (b) or in the absence of additive (a).*

**III. Pathophysiolgy of mental disorders**
Schizophrenic patients exhibit a unique autoimmune reaction against their own platelets. The platelet antigen and its epitope responsible for this reaction have been identified. They provide a basis for a blood test for schizophrenia, which is currently at a final stage of development.
In a recent study, we observed that elevated cortisol which prevails both in stress and depression promotes the synthesis of

the serotonin transporter. This finding offers a novel mechanism which can explain the common state of depression which follows external stress (Fig. 2).

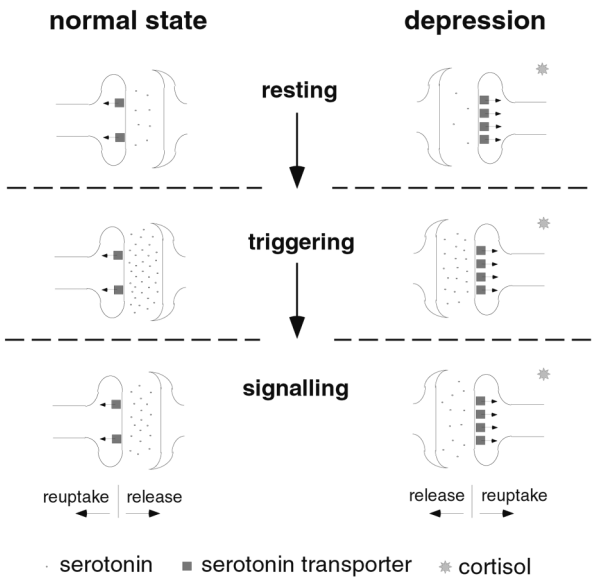


***Fig. 2*** *Hypothetical description of how elevated cortisol in depression can induce reduction of serotonin in the synaptic cleft, both at rest and upon neuronal activation.*

### *Selected publications*


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### *For additional information see:*

www.weizmann.ac.il/Biological_Chemistry/scientist/Shinitzky/meir_shinitzky.html