Effects of Quetiapine on Glucose Metabolism in Cultured Neuronal Cells

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We have found that antipsychotic drugs, such as fluphenazine, chlorpromazine, and the newer atypical drug, clozapine, inhibit glucose transport in neuronal cells (PC12 cell line). These drugs have all been reported to produce hyperglycemia in man and diabetes in some patients, that typically resolves when treatment is discontinued. It may be that the blockade of glucose transport into cells contributes to these abnormalities in glucose metabolism. Generally, dopamine D2 receptor antagonists (such as fluphenazine, pimozide and spiperone) inhibit glucose uptake in our system, whereas D1 antagonists have no effects. Interestingly, glucose transport is not inhibited by all D2 antagonists - haloperidol and sulpiride show marginal effects - therefore, blockade of dopamine receptors may not fully explain the effects of the antipsychotic drugs. We are currently exploring the possibility that the drugs either directly bind to and inhibit the function of glucose transporter (GLUT) proteins or indirectly affect transport by influencing signaling pathways that may involve dopamine receptors or other molecules such as calcium channels. These studies have important implications not only for the regulation of glucose uptake in neurons, but may also relate to the side effects of the antipsychotic drugs which include movement disorders and diabetes. At this juncture, we have begun to profile newer atypical antipsychotics (such as risperidone and olanzapine) with respect to their effects on glucose metabolism in neurons. We would propose to study the effects of quetiapine on glucose uptake and utilization in our model system in comparison to clozapine, risperidone and other antipsychotics. We have developed novel methods of stimulating glucose transport in our cells (by exposure to poly-L-lysine) and have recently produced unique monoclonal antibodies against GLUTs that can be used for these studies. The monoclonal antibodies recognize GLUTs situated at the cell surface and no other reagents like these are available anywhere in the world. We are therefore able to test the effects of antipsychotic drugs on both GLUT-mediated glucose transport and on the expression of GLUTs at the cellular level. It will be interesting to learn if quetiapine also inhibits glucose transport. On the other hand, quetiapine may not interfere so dramatically with glucose uptake, which might suggest it would produce less incidence of hyperglycemia than clozapine (which potently blocks uptake). Given our track record (see recent publications listed below), our established system for studying glucose transport in neurons and the availability of unique reagents, we may be in the best position to help figure out the basis for the hyperglycemic effects of many of the antipsychotic drugs. Moreover, we can determine whether these effects are related to either the therapeutic potential or to the side effects of these drugs.

Objectives

We have reported that a number of antipsychotic drugs (such as clozapine and fluphenazine) that antagonize dopamine at D2 and D4 receptors inhibit glucose transport in neuronal cells. The major objective of these studies will be to compare the effects of quetiapine with the above drugs to determine if inhibition of glucose transport is in some way related to the therapeutic effects of this class of drug. The drugs will be tested for inhibition of glucose transport in our well-established system involving PC12 cells (of rat origin) and in a human neuroblastoma cell line, SY5Y. Theoretically, a drug might block glucose transport by acting (1) directly on the glucose transport protein (GLUT), (2) on some remote signaling event which in turn controls GLUT function, or (3) at the level of GLUT expression. In order to establish that these drugs do not affect the expression of GLUT proteins and their presence in the cell membrane, we will quantify GLUTs using polyclonal antibodies and unique monoclonal antibodies against GLUT3 which have recently been developed in our laboratory.

Goldstein
EXHIBIT NO. 9
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Estimated Budget

Initial characterization of the effects of quetiapine on glucose transport in neuronal cells could be completed within one year. Therefore, we have only proposed a budget for that time frame. If quetiapine has unique effects in this system or it appears worthwhile to differentiate this drug from other antipsychotic medications on the basis of their effects on glucose metabolism, additional studies beyond the first year may be required. The possibility of continuing the project would depend upon the initial results and the interests of the two parties at that time.

A budget of approximately $40,000 would cover the costs for the first year. These funds would mainly be spent on research supplies, some of which are very expensive (e.g., antibody reagents and radiolabeled compounds). A detailed budget breakdown can be provided if there is interest in the project.

Recent publications

1] Dwyer, D.S., Pinkofsky, H., Liu, Y. and Bradley, R.J. Attachment of PC12 cells to adhesion substratum induces the accumulation of glucose transporters (GLUTs) and stimulates glucose metabolism. Neurochem. Res. 23: 1107-1116 (1998).

2] Dwyer, D.S., Liu, Y. and Bradley, R.J. An ethanol-sensitive variant of PC12 neuronal cell line: sensitivity to alcohol is associated with increased cell adhesion and decreased glucose accumulation. J. Cell. Physiol. 178: 93-101 (1999)

3] Dwyer, D.S., Pinkofsky, H., Liu, Y. and Bradley, R.J. Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. Prog. Neuro-Psychopharmacol. and Biol. Psychiat. 23: 69-80 (1999)

4] Dwyer, D.S., Liu, Y. and Bradley, R.J. Dopamine receptor antagonists modulate glucose uptake in rat pheochromocytoma (PC12) cells. Neurosci. Letters 274: 151-154 (1999).

5] Pinkofsky, H., Liu, Y., Bradley, R.J. and Dwyer, D.S. Effects of tricyclic antidepressants on glucose transport in erythrocytes. Life Sci. 66: 271-278 (1999)

6] Dwyer, D.S., Bradley, R.J., Kablinger, A.S, and Freeman, A.M. Glucose metabolism in relation to schizophrenia and antipsychotic drug treatment. Am. J. Psychiat. Submitted.

- immediate drug effects.
  tranquil
  sedation
- hallucinator take several weeks.

2. do immediate effects have anything to do with glucose metabolism
   i.e. hypoglycemia = sedation ??

? cross talk between glucose & DA
  glucose can down regulate DA

→ not weight gain associated with hyperglycemia.