Title ‘Does the association with Diabetes say more about Schizophrenia and its treatment? - the GLUT Hypothesis’

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Abstract

All effective anti psychotic drugs block glucose transporter proteins (GLUTs), peripherally and in the brain. These drugs are implicated in hyperglycaemia as demonstrated in mouse and human studies. Clozapine is the strongest blocker, with Haloperidol the weakest.

The GLUT hypothesis suggests that schizophrenia is partly due to poor functioning of brain glucose transporters (GLUT 1 and 3). Neuronal glucose malnutrition could result in excessive neuronal pruning (so called Crow’s Type 2 with a predominance of negative symptoms) or result in recurrent / ineffective pruning (Type 1 with positive symptoms).

GLUT blockade by anti psychotic agents could assist Type 1 patients to complete the pruning process by deactivating already damaged neurones and circuits, but will make Type 2 patients more cognitively impaired.

Future treatment options are discussed in line with the above formulation.
Introduction

Schizophrenia (initially termed dementia praecox) is a multi dimensional disease featuring 3 syndromes – reality distortion (delusions and hallucinations), disorganisation (inappropriate affect, bizarre behaviour and thought form disorder) and core negative symptoms (poverty of speech, blunted affect and decreased movements). These syndromes, elicited using factor analysis (1), can occur concurrently or, less commonly, individually.

Although descriptions of psychosis and bipolar disorder in adulthood are available throughout the written history of medicine, dementia praecox in adolescents has been described only over the last 120 years; interestingly about 20 – 30 years after sugar became widely available to the population of Europe and Britain (2).

Since 1914 (prior to Chlorpromazine), the positive association between psychosis and hyperglycaemia has been recorded (3). This finding has been subsequently replicated among the first onset drug naive psychosis population (4). Furthermore, there is evidence of increased rates of diabetes mellitus (mainly involving insulin resistance) among first degree relatives of patients with schizophrenia (5).

Schizophrenia and Diabetes

The prevalence of hyperglycaemia in untreated people with schizophrenia has been estimated at around 10% (6). This rises to over 16% when treated with anti psychotic agents (7), with some reversibility when the anti psychotic is stopped. The initial explanation for the finding - that hyperglycaemia was secondary to weight gain or due to the sedentary lifestyle of treated patients - has been questioned by the observation of rapid onset diabetic ketoacidosis in some patients within days of instituting Clozapine (8), the most effective anti psychotic.
Thereafter, Leptin (a hormone produced by fat tissue to dampen appetite) was considered as the causative agent for Clozapine induced hyperglycaemia; but it was subsequently shown that Leptin was simply the distress signature of fat stores being saturated due to excess blood sugar being converted to stored lipids in order to maintain glucose homeostasis.

The alternative theory to explain the rapid onset of hyperglycaemia with Clozapine is the universal property of all anti psychotic agents to block glucose transporters (GLUTs) both within the brain (GLUT 1 and 3), and in the periphery (GLUT 4). Such a blockade would cause hyperglycaemia as shown in mouse studies (9).

Clozapine appears to be the strongest GLUT blocker, followed by Olanzapine, Quetiapine and Risperidone. The weakest GLUT blocker is Haloperidol, with the rest of the ‘typical’ drugs falling in between (10).

**Physiology of GLUT transporters**

GLUTs are a family of funnel shaped transporters, made up of around 150 amino acids, straddling the cell membrane to facilitate diffusion of glucose into the cell. The predominant peripheral GLUT (GLUT 4) is sited mainly in fat and muscle, and is sensitive to insulin. Insulin rapidly shifts intracellular GLUT 4 transporters to the cell membrane when blood glucose rises after a meal.

GLUT 1 and 3 are mainly seen in the brain, but also in placental tissue. These transporters are insensitive to insulin, with the majority of them constantly available at the cell membrane. An increase in these numbers requires a slower process involving messenger RNA, possibly mediated by the ‘brain Insulin’ IGF. GLUT 3 is seen in neurones, and GLUT 1 in endothelial cells. GLUT 3 is predominantly seen in frontal and pre frontal areas of the brain, with GLUT 1 more widespread at the capillary neuronal interface, but particularly present around the thalamus.
GLUT 2 is a Glucose sensor present throughout the body (for example the portal circulation and pancreas) as well as in the hypothalamus in the brain. In conditions of starvation, these sensors relay messages to increase the supply of GLUT 1 and 3, with a reduction of surface GLUT 4. It is likely that in situations of hyperglycaemia, the reverse occurs. On this basis, regular high sugar consumption by patients with schizophrenia would be counterproductive.

**The GLUT Hypothesis**

What is the explanation for higher rates of hyperglycaemia in drug naive first onset psychosis patients?

In 2005, it was hypothesised that schizophrenia was associated with deficits (numbers or function) of the brain GLUTs 1 and 3 – the GLUT Hypothesis (11). As the brain utilises 20 to 50% of available glucose depending on the level of cerebral activity, a state of reduced brain glucose uptake could create a ‘backlog effect’ leading to insulin resistance.

Furthermore, reduced brain glucose uptake would produce cognitive deficits from the start of the psychotic process, as has been observed (12), and show evidence of ‘hypofrontality’ in functional imaging (13). GLUT 1 and 3 deficits would present with the expected features of cerebral hypoglycaemia, including agitation, misperceptions and persecutory ideas, particularly when psychosocial stressors are present, due to unmet neuronal demands for glucose – the predominant nutrient used by the brain.

More damage to cerebral neurones would be expected during further exacerbations of psychosis due to increased demands for glucose, as shown in studies involving serial MRI scanning of recurrently relapsing subjects (14). Deficits in GLUT 1 and 3 would also explain the higher incidence of low birth weight observed in subjects who later develop schizophrenia (15). This is because the placental glucose uptake is via GLUT 1 and 3.
Consequences - Neuronal pruning problems

There are 3 phases of neuronal pruning – an initial phase around the perinatal period, a second phase in late childhood (7 – 11 years) and a third phase specifically involving the frontal / pre frontal cortex in late adolescence or early adulthood. The purpose of pruning is to rationalise neuronal circuits and remove redundant or otherwise damaged neurons and synapses prior to myelination.

GLUT 3 is found predominantly in the frontal / pre frontal area, and GLUT 1 in the thalamus. Any abnormality of GLUT 1 or 3 would provoke excessive or recurrent pruning and consequent grey matter loss in excess of the usual amount. Serial scanning of adolescent children in the process of developing schizophrenia have shown a 4 fold increase in frontal grey matter loss compared to normally developing adolescent peers (16).

Therefore, it could be postulated that schizophrenia is a disorder of abnormal neuronal pruning secondary to pre existing abnormal neuronal development (however caused) as shown in post mortem neuropathology (17). The first stage of excessive pruning in the perinatal period would result in impaired migration and maturation of neurones; the basis for the neuro developmental theory (18). The second phase in childhood would result in general cortical thinning and secondary ventricular enlargement, with the third phase producing excessive thinning specifically in the frontal / pre frontal cortex.

Furthermore, it could be that the Crow’s Types 1 and 2 (19) might be associated with recurrent ineffective pruning causing the Type 1 syndrome with a predominance of positive symptoms (hallucinations and delusions), with excessive pruning causing the Type 2 syndrome, with negative and neurological symptoms.
The connection to the Dopamine Theory

In normal brains, most of the Dopamine produced by the ventral tegmentum (in the brain stem) is supplied to the frontal / pre frontal areas. However in schizophrenia, this supply is largely lost, whilst being supplied in excess to the mesolimbic and striatal sites, possibly due to a feedback process from the frontal lobe to the brain stem to increase production of dopamine. This results in the positive phenomena of hallucinations and delusions. Furthermore, the frontal area supplies the mesolimbic area with glutamate. This supply is also limited in schizophrenia and its normal inhibitory effect on dopamine in the mesolimbic and striatal areas are lost, thereby perpetuating psychosis (20). The loss of frontal connections with the thalamus, basal ganglia and cerebellum would result in problems with executive functioning. The loss of glutamate is similar to the effects of PCP (a Glutamate NMDA receptor inhibitor) which produces a syndrome similar to schizophrenia clinically (21). Therefore, it could be postulated that the over supply of Dopamine and undersupply of glutamate is secondary to intrinsic deficits in function of the frontal / pre frontal areas.

Direct Evidence for the GLUT hypothesis and future research strategy

There has been some investigation of brain GLUT function (including effects of GLUT blockers) mainly involving mouse studies. Mice deficient in GLUT 3 have shown perturbed social behaviour, reduced vocalisation and abnormal cognitive flexibility with intact gross motor ability – which the authors considered to be akin to autistic spectrum disorder (22). GLUT 1 deficiency is noted to produce significant brain damage in mice and humans. GLUT blockade with antipsychotic drugs produces a reactive hyperglycaemia in mouse studies (9).

Positron Emission Tomography (PET) studies in humans utilising ligands (monoclonal antibodies) binding to GLUT 1 and 3 would be the next step to further investigate the GLUT theory. From a genetic viewpoint, genes coding for
GLUT 1 and 3 could be studied in association with the currently known (but rare) genetic markers for psychosis, with particular emphasis on chromosome 1q21-25, a region common to diabetes and psychosis risk (23). With regards to the study of mice deficient in GLUT 3, it would be helpful to check them for hyperglycaemia.

The alternative to the GLUT theory is possible deficits in the brain Insulin signalling system, involving IGF 1 (including its receptor), and Akt / Glycogen synthesis pathways within the neurones (24)

**Future treatment options**

There is some evidence that some anti psychotic drugs (the stronger GLUT blockers) could protect the cortex from further thinning associated with recurrent or chronic schizophrenic symptoms (25). Whether this translates to clinically meaningful improvements remains to be seen, and will require studies of longer duration (i.e. over 2 years) involving psychometric and imaging follow up. The actual dosage required in the longer term to provide this protective effect is also unclear, but clinically relevant to avoid unnecessary side effects (including diabetes and endocrine complications of longer term use).

The other option currently being considered is using Metformin and other anti diabetic drugs to reduce hyperglycaemia and obesity when treating schizophrenia with anti psychotic agents. Perhaps Metformin could be considered for prophylactic use in patients who are already at risk of metabolic side effects (26).

Glutamate enhancers remain the most realistic medium term option (27), if the usual toxicity of glutamate agonists could be avoided. Furthermore, limiting beta amyloid in the brain, using drugs such as the secretace inhibitors, could increase the uptake of glutamate in to neurones, providing functional enhancement of glutamate in the mesolimbic area (28). From a GLUT view point, perhaps a selective GLUT 2 blocker, by mimicking hypoglycaemia, could increase the available GLUT 1 and 3 in the brain, improving cognition and possibly the other features of schizophrenia by reversing the process of ‘hypofrontality’.
Conclusions

The pathophysiology of schizophrenia has involved a long running debate between the neuro developmental and neuro degenerative camps, with the latter making a comeback of late, and with the concept of dementia praecox gaining renewed attention. The GLUT theory (and its alternatives) suggests that both play a part to produce the observed findings described above as well as the imaging findings (for a review see 11).

Hopefully new drugs, such as glutamate enhancers, can avoid the cardiovascular and diabetic risks, thereby improving adherence which remains the biggest problem for clinicians. Better biological understanding, with clarity in explanations regards the pathophysiology of schizophrenia, will also help adherence.

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