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Schizophrenia is a Diabetic Brain State: An Elucidation of Impaired Neurometabolism

R.J. HOLDEN* and P.A. MOONEY*

**Associate Professor, Medical Research Unit, University of Wollongong, Northfields Avenue, Wollongong 2522 NSW, Australia and † Senior Lecturer, Dept. of Applied Biomedical Science, University of Tasmania at Launceston, P.O. Box 1214, Launceston 7250, Tasmania*

Abstract — In this paper a detailed argument will be advanced in support of the notion that schizophrenia is fundamentally a diabetic brain state, henceforth referred to as 'cerebral diabetes'. Many extraneous features of cerebral diabetes have been observed, including positron emission tomography (PET) scans which reflect abnormal distribution patterns and diminished supplies of glucose in the brain. Equally, empirical research has demonstrated that plasma levels of essential fatty acids and prostaglandins are abnormally low, and low levels of glycoproteins in the urine of cerebral diabetics have also been observed. In addition, cerebral diabetics manifest a wide range of disturbing physical symptoms, such as, impaired sexual function, temperature control, low blood pressure, disrupted sleep patterns, excessive thirst, poor memory, insensitivity to pain, and chronic unhappiness, all of which can be attributed to disrupted neuroendocrine function. Thus, in order to persuasively assert the redefinition of schizophrenia as 'cerebral diabetes', we shall first explicate glucose regulation and transport in the brain and then outline how this interacts with essential fatty acids and prostaglandins, neurotransmission, and the neuroendocrine system. In so doing, we shall provide a metabolic explanation for all the prominent symptoms currently known to be associated with cerebral diabetes and indicate some future therapeutic interventions.

Introduction

Prior to the introduction of phenothiazines in 1959, insulin coma therapy (ICT) was the treatment of choice for those patients suffering from paranoia, catatonia, hebephrenia, mixed forms of schizophrenia, schizoaffective depressed conditions, and anxiety states both neurotic and psychotic. The long term effect of ICT was reputedly more permanent and durable than that currently achieved by neuroleptics. That this treatment regime has fallen into disfavour, Laqueur finds regrettable but, like so many psychiatric interventions, the reason underlying the effectiveness of insulin coma therapy in the treatment of schizophrenia has, thus far, remained obscure (1).

Laqueur and LaBurt (2) documented the clinical effectiveness of ICT in Creedmoor State Hospital from 1951–1957 in which the principle technique utilized was to gradually administer a sequential series of low insulin doses over a period of time. Each patient received between 10–50 ICTs during the course of their hospitalization in response to which a discharge rate of 88.2% was obtained. Given the historical period in which this treatment was administered, such results could be regarded as a considerable clinical achievement. A strict dietary regimen was introduced

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in conjunction with multiple dose insulin coma therapy which produced a superior treatment outcome to single large dose ICT. Although the positive treatment response obtained by ICT was not well understood during its period of use (1920–1960), there was some empirical endorsement supporting its effectiveness. For example, some schizophrenics who were both hyperglycaemic and insulin resistant, were considered to have a good prognosis, capable of either spontaneously remitting or recovering following ICT (3). In a contemporary parlance, such patients would be regarded as having positive schizophrenia – a perception which will be discussed later. Himwich (4) reported a significant increase in serotonin in the hippocampal region following insulin-induced hypoglycaemia, with a concomitant decrease in acetylcholine – the latter of which has since been contradicted by current researchers. Finally, although Dussik (5) foreshadowed the abandonment of ICT in favour of neuroleptics, he also recognised the 'unique' potential of insulin as a therapeutic tool due to its capacity to tranquillise and/or reactivate psychotic patients.

In the forthcoming paragraphs the regulation and transport of glucose in the brain will be outlined together with the interaction this has with neurotransmission and the neuroendocrine system; the dopamine hypothesis will be re-examined together with the interplay that exists between dopamine, glucose metabolism, essential fatty acids, and the prostaglandins. Finally, an argument will be advanced that reconceives schizophrenia as 'cerebral diabetes' in the course of which the therapeutic potential of insulin will be indicated together with an explanation of its probable psychiatric effectiveness.

Schizophrenia, glucose metabolism, and neurotransmission

It is now becoming clear that insulin and/or insulin-like growth factor 1 (IGF-1) serve a critical role in normal brain metabolism. p21ras is a regulatory protein expressed by the H-ras oncogene. Insulin is involved in the conversion of p21ras.GDP (the inactive form) to p21ras.GTP (the active form) which implies that p21ras is a central component of the insulin signal transduction pathway (6). This means that if insulin levels are depleted, p21ras would remain in its inactive form which would, in turn, reduce the availability of tetrahydrobiopterin (BH4), diacylglycerol (DAG), and protein kinase C (PKC). In Figure 1, it can be seen that any reduction in the levels of BH4 will negatively impact on the activity of: (i) tyrosine hydroxylase (TH) which initiates the metabolism of the catecholamine chain through the conversion of m-tyrosine to dopa (7); (ii) tryptophan hydroxylase (TPH), which initiates the metabolism of the serotonergic pathway (8); and (iii) the release of acetylcholine (ACh), dopamine (DA) (9), and serotonin (5HT) (10) neurotransmitters. In addition, any reduction in levels of dopamine will also impact on the neuroendocrine system since dopamine initiates the release of the hypothalamic releasing hormones (11).

It is now known that insulin receptor binding stimulates the production of diacylglycerol which, in turn, activates protein kinase C (PKC) (12). Insulin has also been shown to provoke the translocation of PKC from the cytosol to the membranes in rat skeletal muscle which results in increased glucose uptake and utilisation (13). Of equal importance is the fact that insulin-like growth factor (IGF-1) is involved in the proliferation of astrocytes in the adult brain via the translocation of PKC from the cytosol to the membrane fraction. It has been observed that rapid mobilisation of calcium (Ca^{2+}) occurs in response to both IGF-1 and insulin, and it has been hypothesised that changes in levels of intracellular Ca^{2+} may constitute a PKC-independent intracellular pathway in relation to the IGF-1 stimulated astrocyte proliferation (14).

Nori et al (15) have demonstrated that the GTPase activating protein (GAP) negatively regulates p21ras 'by enhancing its intrinsic GTPase activity'. Thus, overexpression of GAP will cause p21ras to remain in its inactive GDP-bound form which would interfere with the PKC-dependent signal transduction pathway since this requires p21ras in its active GTP-bound form for full transmission. Further, when GAP is overexpressed and p21ras remains in its inactive GDP-bound form, effective glucose transport and neurotransmission will be compromised by reducing the activity of DAG, PKC and BH4 respectively. Consequently, any breakdown in neurometabolism that induces an overexpression of GAP will seriously interfere with glucose transport and the activity of tyrosine and tryptophan hydroxylases. Such overexpression of GAP could be caused by low levels of prostaglandins (PGE_2 , $PGF_{2\alpha}$) since these deactivate ras.GAP (16). Should these prostaglandin levels be low for some reason, then ras.GAP would not be deactivated and thus GAP would be overexpressed. If this biochemical event also occurred in conjunction with low insulin levels, then the capacity for insulin to effect the conversion of p21ras from the inactive GDP-bound form to the active GTP-bound form would be seriously impaired. In addition, since GAP negatively regulates p21ras (17), overexpression of GAP will seriously impair p21ras activity. Any impairment of p21ras activity will negatively impact on insulin and

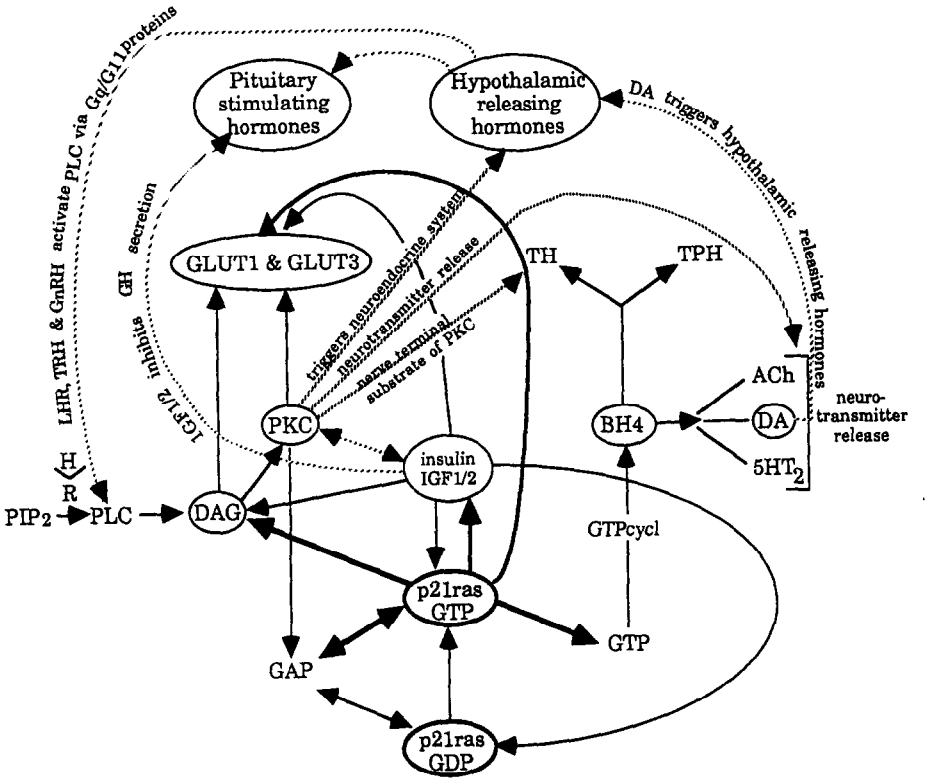

Fig. 1 Showing the interaction between glucose regulation and transport, neurotransmission, and the neuroendocrine system. Abbreviations:(TH) tyrosine hydroxylase, (TPH) tryptophan hydroxylase, (ACh) acetylcholine, (DA) dopamine, ($5HT_2$) serotonin, (BH4) tetrahydrobiopterin, (GTPcycl) GTP cyclohydrolase, (GAP) GTP-ase activating protein, (DAG) diacylglycerol, (PKC) protein kinase C, (GLUT 1-3) glucose transporters 1&3, (PTH) parathyroid hormone, (PIP_2) phosphatidylinositol 4, 5-bisphosphate, (PLC) phospholipase C, (H>R) hormone receptor, (LHR) luteinizing releasing hormone, (TRH) thyrotrophin releasing hormone, (GnRH) gonadotrophin releasing hormone, (GH) growth hormone, (IGF1/2) insulin-like growth factor.

IGF-1 and, therefore, on glucose transport and regulation; the PKC-dependent signal transduction pathway via DAG; facilitative diffusion of glucose into the cells via GLUT1 and GLUT3; levels of BH4 due to inactivated GTP-cyclohydrolase, the rate-limiting enzyme in the biosynthesis of GTP to BH4; and a reduction of intracellular GTP levels which also significantly inhibits BH4 biosynthesis (18).

Recently, de Vries-Smits et al (19) have argued 'that p21ras is emerging as an important mediator of insulin signalling'. Whilst this group reinforces the role of insulin and growth factors in converting inactive GDP-bound ras to active GTP-bound ras, they have also identified p21ras as a primary mediator of the glucose regulation and transport. In this study it was found that p21ras plays an intrinsic role in mediating insulin and platelet-derived growth factor (PDGF) activation of extracellular signal-regulated kinase 2 (ERK2). But while p21ras mediates insulin and PDGF activation of ERK2, nerve growth factor (NGF), epidermal growth factor (EGF), insulin, and IGF-1 can induce activation of p21ras (20) – an activation process that involves the tyrosine kinases which initiate and terminate cell growth and division (21). Since NGF, EGF, and fibroblast growth factor (FGF) receptors possess intrinsic tyrosine kinase activity (22) these growth factors also play a major role in cell signalling and p21ras activity. This process has been further clarified by Porras et al (23) who found that activation of the insulin receptor, tyrosine kinase, induced rapid activation of p21ras which, in turn, initiated cytosolic mitogen-activated protein (MAP) kinase activity, also known as extracellular signal-related kinase (ERK). So while p21ras activates the insulin-Ras signalling pathway, insulin converts inactive GDP-bound p21ras to active GTP-bound p21ras which then mediates MAP kinase activity. It has also been found by Porras et al that 'Ras can efficiently substitute for insulin in activating myelin basic protein (MBP) kinase(s)' which effectively means that

Ras mediates between insulin binding and MBP activation. In summary, p21ras.GTP activates insulin which then converts inactive p21ras.GDP to active p21ras.GTP. In addition, p21ras can substitute for insulin by increasing DAG levels and, thereby, indirectly influencing the activity of PKC (22). But p21ras can also mimic the action of insulin and induce glucose transporter translocation which means that this protein product can also influence the activity of the glucose transporters directly (24). Finally, p21ras causally interacts with GAP, the latter being both a regulator and downstream target of p21ras (25).

The remaining step to be explicated with respect to glucose regulation and transport is the interaction between PKC (which is activated by both DAG and insulin) and the glucose transporters. Protein kinase C is of vital importance in this connection since it links glucose metabolism with the neuroendocrine system (26–28), neurotransmitter release (29,30), and tyrosine hydroxylase (TH) which is one of four nerve terminal substrates of PKC (30). Thus, if either insulin levels are low or p21ras remains in its GDP-bound form, then DAG availability and, consequently, PKC activity would be seriously restricted. This would then compromise the release of the hypothalamic releasing hormones, neurotransmitter release, as well as the expression of GLUT1 and 3.

Lienhard et al (31) recently identified the role glucose transporters play in the transportation of glucose into the cells. The glucose transporters particularly relevant to brain glucose metabolism are GLUT1, which specialises at the level of the blood-brain barrier, and GLUT3 which specialises in the transportation of glucose into neuronal cells. In muscle cells, GLUT1 and GLUT4 act in a dynamic relation to each other. In diabetic rat skeletal muscle, hyperglycaemia (in the presence of normoinsulinaemia) caused a reversible decrease of GLUT4 with a simultaneous increase of GLUT1 in the plasma membrane, and a decrease of both glucose transporters (GLUT4 and GLUT1) in the intracellular membrane. It has also been reported that GLUT1 expression increases in the erythrocytes of non-insulin dependent diabetes mellitus (NIDDM) patients in the presence of hyperglycaemia and normoinsulinaemia (32). Of equal interest is the response of glucose transporters to a state of hypoglycaemia. Hundal et al (33) have found that the subcellular distribution of GLUT1 is influenced by both insulin and IGF-1, and that the oral hypoglycaemic drug, metformin, causes an increase of GLUT1 in the plasma membrane and a reduction of GLUT1 in the internal membranes. Thus, the response of GLUT1 to induced hypoglycaemia is the same as that found in hyperglycaemia, namely, the content of GLUT1 in the plasma membrane increases, causing a corresponding decrease in the intracellular membrane. In addition, it has been found that levels of GLUT1 are elevated in response to hypoxia which immediately induces a rapid increase in glucose transport (34). Thus, in response to hyperglycaemia, hypoglycaemia, and hypoxia levels of GLUT1 increase in the plasma membrane in muscle cells. These findings are also supported by Boado and Pardridge (35) who examined the hypoglycaemic response of GLUT1 in bovine brain capillary endothelial cells. Here, it was similarly found that glucose deprivation caused a dose and time dependent increase in GLUT1 abundance in the blood brain barrier which is thought to be mediated by PKC-dependent mechanism.

Indeed, the above suspicion, that glucose transporters are mediated through a PKC-dependent mechanism, is partially supported by the observations of Rapoport et al (36). This group investigated the thymic T cell anergy in nonobese diabetic mice and found that PKC activity was reduced and p21ras activation was deficient. The deficiency in p21ras activation was associated with a commensurate reduction in GTP-bound p21ras, possibly due to the effect of low levels of insulin/IGF-1 thereby maintaining p21ras in its inactive GDP-bound form (6,22). However, it is now known that while GLUT1 and GLUT4 normally transport glucose into muscle cells through facilitative diffusion, GLUT1 is also insulin responsive and, therefore, can be regulated by acute mechanisms (37). Thus, active GTP-bound p21ras, which mimics the action of insulin on glucose transport translocation (24), is also capable of regulating the activity of GLUT1 directly. But since the active GTP-bound p21ras: (i) mimics the insulin action on glucose transporter translocation (24); (ii) influences the activity of insulin and IGF1 (38); and (iii) activates the DAG, PKC pathway (39,40); all of which can all directly influence the activity of the glucose transporters, it is not surprising that a deficiency in p21ras.GTP leads to a reduction in glucose transporter activity. Finally, although GLUT1 specialises at the level of the BBB and GLUT3 specialises in neuronal cells, the distribution of GLUT3 alters from species to species. In the monkey brain, 'GLUT3 is most highly expressed in the frontal lobe of the cerebrum, whereas GLUT1 is most abundant in the basal ganglia and the thalamus. Moderately higher GLUT3 mRNA levels were detected in the parietal lobe of the cerebrum, hippocampus, and cerebellum than levels of GLUT1 transcripts' (41:470). This observation may have an important bearing on the abnormal distribution pattern of glucose observed in positron emission tomography (PET) scans of schizophrenic

patients (42), mood lability, and central monoamine dysfunction, about which more will be said later.

In summary, p21ras is the pivotal link between glucose regulation and transport and central neurotransmission. p21ras is a protein product produced by the Harvey-ras oncogene which is contained on the short arm of chromosome 11 – a chromosomal position which has been implicated in the genetics of affective disorders (43) and, more recently, the H-ras oncogene itself has been implicated in Type I diabetes (44). Since both diabetes and schizophrenia are illnesses that have definitive familial tendencies, it seems probable that the initial source of dysfunction lies with the H-ras oncogene and, more specifically, with p21ras. As can be seen from Figure 1, if the activity of GTP-bound p21ras is low, then the levels of insulin, DAG, and PKC will also be negatively affected and cause p21ras to predominantly remain in its inactive GDP-bound form due to diminished supplies of insulin. It also means that glucose transporter activity will be compromised which is particularly problematic for GLUT3 since this specialises in the neuronal cells and is most abundant in the prefrontal cortex. This could well account for the persistent hypofrontality found in both schizophrenia and unipolar depression (42) in which glucose uptake is virtually nonexistent. However, gross impairment of the active form of GTP-bound p21ras will also negatively impact on neurotransmission since GTP activates GTP-cyclohydrolase which in turn stimulates the synthesis of tetrahydrobiopterin activity. Since tetrahydrobiopterin in involved in the release of neurotransmitters, such as, acetylcholine, serotonin, and dopamine, (dopamine also triggers the hypothalamic releasing hormones (11)) and modulates the activity of tyrosine and tryptophan hydroxylase (which controls the catecholamine and serotonergic pathways), any depletion of BH4 levels will have serious consequences with respect to normal neurotransmission and the neuroendocrine system. In fact, since both dopamine and PKC serve as triggers to the hypothalamic releasing hormones, diminished availability of either DA or PKC will negatively impact on the neuroendocrine system.

It has been reported that plasma levels of tetrahydrobiopterin are deficient in unipolar and bipolar depressed patients and that these levels rapidly increase as the patient shifts into mania (45). In addition, it has also been found that serum tetrahydrobiopterin levels are lower in Alzheimer patients compared to schizophrenics, but both are lower compared to normal controls (46). This observation has been further endorsed by Anderson et al (47) who reported decreased availability of BH4 in the serum, CSF, and post-mortem brain of Alzheimer patients. Equally, BH4 deficiency has also been found in serum, CSF, and post-mortem brain of Parkinson's disease patients which was also associated with low CSF homovanillic acid (HVA) levels. Anderson et al found that electroconvulsive therapy (ECT) stimulated BH4 production in psychotically depressed patients, a finding also supported by other studies. Hossain et al (48) found that repeated electroconvulsive shock (ECS) (one per day for 7 days) resulted in elevated levels of BH4 in locus coeruleus, hippocampus, frontal cortex, hypothalamus, ventral tegmental area, and adrenal gland in the rat. They also found that GTP-cyclohydrolase activity was significantly increased in all areas above mentioned with the exception of the ventral tegmental area (VTA). While the VTA is predominantly a dopaminergic (and less significantly a serotonergic) cell body region, the other brain areas are predominantly noradrenergic with the exception of the frontal cortex which is both dopaminergic and noradrenergic.

In a subsequent study, Housain et al (49) found that haloperidol and ECS elevated levels of BH4 in the nigrostriatal system of 6-hydroxydopamine lesioned rats. Finally, Hamon et al (50) found that insulin-induced hypoglycaemia is associated with reduced levels of BH4 due to decreased dihydropteridine reductase (DHPR) activity. Because streptozotocin-induced diabetes corresponded to a total decrease in biopterin biosynthesis in the rat brain, it was postulated that a reduction in the BH4 cofactor, which negatively affects neurotransmitter formation and release, would be sufficient to cause a decrease in intellectual performance associated with juvenile onset diabetes and Alzheimer's disease in which BH4 biosynthesis is known to be deficient (50). This line of reasoning also applies to negative or chronic schizophrenia since the same set biochemical parameters obtain. This proposition is also consistent with recent research which has shown that severe suicidal and homicidal behaviour is associated with mild hypoglycaemia and low serotonin metabolite levels of 5-hydroxyindoleacetic acid (5-HIAA) in the CSF (51).

These studies serve to confirm the view that maintaining the integrity of the BH4 pathway is vitally important for effective neurotransmission. But the neuroendocrine system is also linked to the BH4 pathway due to the fact that dopamine triggers the release of the hypothalamic releasing hormones (11). This means that there is some indirect cross-talk between dopamine and PKC which also serves the same function. In turn, the thyrotrophin-releasing hormone (TRH) and the gonadotrophin-releasing hormone (GnRH) receptors activate phospholipase C (PLC) by coupling to the Gq and/or G11 proteins, while the luteinizing hormone receptor (LHR) acti-

vates two intracellular signalling pathways: one increases cyclic AMP (cAMP) and the other activates PLC (52,53). PLC, in turn, increases the levels of DAG which activates PKC. Thus, there is an interconnecting sequence of metabolic events from PKC to the hypothalamic releasing hormones to PLC, DAG, and PKC. Consequently, any decrease in PKC activity, caused by either low GTP-bound p21ras or insulin would down regulate the entire sequence of the PKC cycle which would result in profound physiological change, including that of impaired neurotransmitter release. There is also another connection between IGF-1 and the neuroendocrine system in that IGF-1/2 inhibits growth hormone secretion from the pituitary (54).

The dopamine hypothesis revisited

Horrobin (55) has implicated essential fatty acids (EFAs) and prostaglandins (PGs) in the pathophysiology of schizophrenia – a direction of empirical research that resulted from the observation that neuroleptics stimulated prolactin secretion which is necessary for the conversion of essential fatty acids to prostaglandins. This is interesting since it is now known that withdrawal of dopamine stimulates prolactin secretion together with the prolactin releasing action of thyrotropin releasing hormone (TRH). In addition, dopamine withdrawal, which is mediated by the activation of protein kinase A, also increases intracellular cAMP, and induces protein kinase A, protein kinase C, and phospholipase C activation (56). This means that excess levels of dopamine, thought to be associated with schizophrenia, will inhibit prolactin secretion and hence the conversion of essential fatty acids to their prostaglandin metabolites (55). But excess levels of dopamine would also down regulate protein kinase C and phospholipase C. Down-regulation of PKC would inhibit the activity of the glucose transporters and, in this connection, GLUT3 is of particular interest since this transporter is highly expressed in the prefrontal cortex. Equally, down-regulation of PLC will cause a reduction in the synthesis of arachidonic acid (AA) which produces prostaglandins PGE_2 and $PGF_{2\alpha}$ (11) known to be responsible for deactivating ras.GAP (16,57), and stimulating the activity of PKC (see Fig. 2).

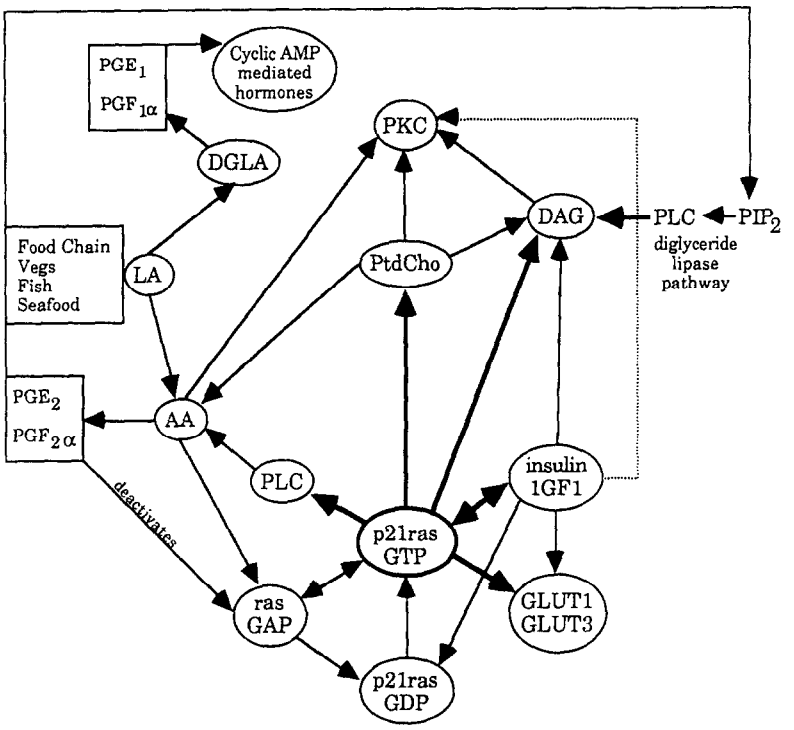

Fig 2. Showing the interaction between essential fatty acids, prostaglandins, and glucose regulation and transport. Abbreviations: (PKC) protein kinase C, (DAG) diacylglycerol, (AA) arachidonic acid, (LA) linoleic acid, (DGLA) dihomogamma linolenic acid, ($PGE_{1,2}$) ($PGF_{1,2\alpha}$) prostaglandins, (PIP_2) phosphatidylinositol 4,5-bisphosphate, (PLC) phospholipase C, (PtdCho) phosphotidylcholine, (GLUT1) and (GLUT3) glucose transporters 1 and 3.

Thus, excessive levels of dopamine will result in serious impairment of PKC activity due to the absence of stimulation from prolactin, arachidonic acid, and phospholipase C. But since $PGE_2$and $PGF_{2\alpha}$ are involved in the deactivation of ras.GAP, this means that excess dopamine levels will result in low prostaglandin levels, due to the inactivity of prolactin and, thus, the deactivation process will not occur. This will result in GAP being overexpressed in which case GDP-bound p21ras will remain in its inactive form thereby creating an internally reinforcing inhibitory loop, since this will inhibit the conversion of inactive GDP-bound p21ras to active GTP-bound p21ras. As such, the effects on both glucose metabolism and neurotransmission would be metabolically disastrous.

It is well documented in the literature that the dopamine hypothesis is highly equivocal with some studies reporting elevated levels of dopamine and others that dopamine is diminished (58). That dopamine levels are elevated is supported by the clinical observation that neuroleptics decrease dopamine activity and concomitantly improve schizophrenic symptoms, while drugs that increase dopamine activity exacerbate schizophrenic symptoms (59). The confusion that currently exists surrounding the 'dopamine hypothesis' could well be attributed to a failure to distinguish between the positive and negative symptoms of schizophrenia. Lohr and Flynn (60) have observed that neuroleptics are more effective in containing the positive symptoms of schizophrenia (associated with hyperdopaminergia) than the negative symptoms (associated with hypodopaminergia) – an observation supported by the fact that amphetamines, which increase dopamine activity, improve the negative symptoms of schizophrenia. In addition, nicotine modulates the release of several neurotransmitters, norepinephrine, acetylcholine, serotonin, and dopamine, particularly in the nigrostriatal and mesolimbic systems. It is thought that the action of nicotine on the dopaminergic pathway may account for the high incidence of smoking behaviour among schizophrenic patients. This notion is supported by Sandyk and Kay (61) who found that early onset of schizophrenia was associated with prominent negative symptoms, a high incidence of smoking behaviour, decreased dopamine activity, low plasma follicle stimulating hormone (FSH) levels and higher doses of neuroleptics compared to nonsmoking schizophrenic controls. It has also been found that smoking schizophrenics who receive higher neuroleptic doses than nonsmoking schizophrenics, are more prone to tardive dyskinesia (62,63).

One complicating factor concerning the influence of nicotine on dopamine activity is that heterocyclic amines (HCAs) are also present in the smoke of cigarettes which not only inhibit the action of tyrosine and tryptophan hydroxylase, tetrahydrobiopterin, type A monoamine oxidase (MAO), aromatic-L-amino-acid carboxylase (AADC), but HCAs also have the effect of blocking dopamine reuptake (64). Thus, the interaction of heterocyclic amines, nicotine, and dopamine complicates the dopamine hypothesis for, while nicotine increases dopamine activity, heterocyclic amines inhibit dopamine activity and thus a vicious cycle ensues. (The causal role that HCAs play in the etiology of schizophrenia has been outlined in a previous paper (65)).

In summary, there are two possible hypotheses concerning dopamine: (i) that elevated levels of dopamine, associated with positive schizophrenia, inhibit prolactin secretion and thus the EFA/PG conversion leading to an overexpression of ras.GAP and down-regulation of the PIP2, PLC, DAG, PKC, GLUT1/3 pathway; and (ii) that depleted levels of dopamine, associated with negative schizophrenia, possibly result from genetic aberrations of p21ras such that p21ras remains in its inactive GDP-bound form, leading to low BH4 biosynthesis and, thereby, compromising neurotransmitter release and production. Such genetic abnormalities may be specific to the H-ras oncogene which is already implicated in Type 1 diabetes or, a posttranscriptional defect of the protein product itself. This would then be compounded by low insulin levels since active ras.GTP stimulates insulin that directly influences the activity of PKC, the glucose transporters, and converts p21ras.GDP to p21ras.GTP. Thus, on this hypothesis, both positive and negative schizophrenia would result in the down-regulation of PKC, PLC, and glucose transporter activity; depleted levels of BH4 thereby disrupting neurotransmission; and a functionally impaired neuroendocrine system.

From Figure 2 it can be seen that linoleic acid (LA), an essential fatty acid found in vegetables, fish, and seafood, is converted to dihomogamma linolenic acid (DGLA) and arachidonic acid (AA) each of which are converted to prostaglandins – PGE_1, $PGF_{1\alpha}$ and PGE_2, $PGF_{2\alpha}$ respectively (11). While PGE_1 and $PGF_{1\alpha}$ stimulate the activity of the cyclic AMP mediated hormones (11), PGE_2 and $PGF_{2\alpha}$ deactivate ras.GAP which prevents GAP from being permanently overexpressed (57). This is important since overexpression of GAP causes p21ras to remain in its inactive GDP-bound form. But PGE_2 and $PGF_{2\alpha}$ also stimulate the activity of phosphatidylinositol 4.5-bisphosphate (PIP_2) which activates the PLC, DAG, PKC pathway (66). Thus low levels of these prostaglandins will also reduce PKC availabil-

ity and, hence, glucose transporter activity. Interestingly enough, Horrobin has reported reduced levels of LA in plasma phospholipids in schizophrenic patients in the UK and Japan (55), and has therefore advanced the view that schizophrenia could be due to a prostaglandin deficiency (67). In addition, Glen et al (68) endorse the view that positive and negative schizophrenia are two distinct disease processes. They found that positive schizophrenics had normal fatty acid levels in the membranes while negative schizophrenics had abnormal fatty acid levels, a difference which could not be attributed to neuroleptic medication. Finally, it has been observed that schizophrenics are insensitive to pain, rheumatoid arthritis and other inflammatory diseases (55). In fact, it is now known that rheumatoid arthritis is associated with excessive protein kinase C activity (Horrobin, personal communication, 1993). Thus, if our thesis is correct, that in both positive and negative schizophrenia there is a significant reduction in PKC activity, then the apparent protection against developing such inflammatory diseases can be explained.

Yet another interesting observation that distinguishes positive and negative schizophrenia has been made by Sandyk and Kay (69). They found a significant correlation between early onset of schizophrenia, negative symptomatology, and the subsequent development of drug induced parkinsonism. In addition, they postulate a relationship between early onset of schizophrenia and hypothalamic damage thereby providing a basis for schizophrenia as a post-pubertal disorder. Furthermore, it was also observed that low plasma FSH levels are associated with early onset of schizophrenia and negative symptoms. However, given that Parkinson's disease is associated with depleted levels of dopamine in the nigro-striatal region, and that dopamine, PKC and PGE_1 trigger the hypothalamic releasing hormones (11), it is not unsurprising that hypothalamic dysfunction is present in negative schizophrenia. This is because negative schizophrenia is strongly associated with hypodopaminergia resulting from low BH4 levels, a collapse of the PKC signal transduction pathway, and low prostaglandin levels which also induce neurotransmitter release (11) and release of the hypothalamic releasing hormones (see Figure 3). In addition, FSH is a glycoprotein hormone mediated by cyclic AMP and dependent on PGE_1 and $PGF_{1\alpha}$ for activation, thus, low plasma levels of linoleic acid (known to be associated with schizophrenia (55)), can account for this observation due to impairment of the LA—DGLA—PGE_1/$PGF_{1\alpha}$ pathway.

From Figure 3, it can be seen that PGE_1/$PGF_{1\alpha}$ also depresses adrenergic responses (11) which, if impaired through low prostaglandin levels, could conceivably result in high adrenergically induced anxiety commonly associated with psychosis. Thus, a PGE_1/$PGF_{1\alpha}$ deficiency can result in the impairment of neurotransmitter release; hypothalamic hormonal function; hypothalamic releasing hormones that activate the PLC—DAG—PKC pathway; while a PGE_2/$PGF_{2\alpha}$ deficiency can result in impairment of the PIP_2—PLC—DAG—PKC pathway (see Fig. 3). Of equal importance, however, is the AA—GAP, PGE_2/$PGF_{2\alpha}$—GAP circuit (see Fig. 2) as this negatively impacts on p21ras activity which is the central pivot for glucose regulation and transport, and the EFA, and PG pathways. But p21ras also increases phosphatidylcholine (PtdCho) turnover, the hydrolysis of which serves to elevate levels of DAG and, hence, also indirectly modulates the activity of PKC (see Fig. 2). However, phosphatidylcholine also produces arachidonic acid from which PGE_2/$PGF_{2\alpha}$ are produced, both of which are capable of elevating PIP_2 hydrolysis (which initiates the PLC—DAG—PKC pathway) and cAMP accumulation (70). In addition, Price et al (70) (Fig. 2) suspected that p21ras activates PKC through a mechanism that was independent of DAG. PKC was subsequently found to be modulated by arachidonic acid and PtdCho, the latter of which is now thought to be the main source of DAG. It was further reported by Price et al that arachidonic acid release could be due to activation of the phospholipase C/diglyceride lipase pathway, emanating from p21ras. Once again it can be seen that excess dopamine, which leads to overexpression of GAP and causes p21ras to remain in its inactive GDP-bound form, ultimately induces the collapse of the insulin/PKC signal transduction pathway and inhibits PLC activation of arachidonic acid release causing low availability of PGE_2/$PGF_{2\alpha}$ (see Fig. 2). However, because these prostaglandins deactivate GAP, failure of the deactivation process will further compound the overexpression of GAP and reduced availability of the active form of GTP-bound p21ras.

In essence, the combined effect of p21ras remaining in its inactive GDP-bound form, operating in association with decreased PKC and glucose transport activity, initiates a complicated metabolic chain reaction which can account for most of the known metabolic symptoms associated with positive and negative schizophrenia (see Table 1). Even elevated levels of dopamine could be understood as a compensatory metabolic mechanism designed to overcome the effects of decreased PKC activity. However, it has been reported that a physiological antagonism exists between dopamine and PGE_1, which means that a PGE_1 deficiency could conceivably cause an increase

Table 1 Showing common symptoms of schizophrenia, the hormones and neurotransmitters implicated with their associated causes

Symptoms	Neurotransmitters/ hormones	Causes
1. Impaired sexual function Disrupted sleep	Gonadotrophin releasing hormone	Low PKC Low PGE_1
2. Impaired temperature control	Thyrotrophin stimulating hormone	Low PKC Low PGE_1
3. Low blood pressure Excessive thirst	Hypodopaminergia	Low BH4
4. Insensitivity to pain Chronic unhappiness	Low serotonin levels	Low BH4
5. Disrupted sleep Poor memory	Low acetylcholine levels	Low BH4
6. Insensitivity to pain	Low insulin levels	Low p21ras.GTP availability
7. High anxiety – fight/flight behaviour	High adrenalin levels	Low PGE_1

Adapted from *The Fabric of Mind* by R. Bergland (Penguin, Harmondsworth, 1985).

in dopamine activity (55). Unfortunately, the elevation of dopamine would also inhibit dopamine withdrawal in conjunction with prolactin secretion and activation of PLC, PKA, and PKC. Thus, both sustained increases and decreases in dopamine levels will lead to impaired glucose transport and utilisation.

Whilst the proposition that there could be two different states of schizophrenia: hypodopaminergia (negative schizophrenia) and hyperdopaminergia (positive schizophrenia) has been signalled by other authors (59,68,71), the outcome is, unfortunately, the same in both cases but for independently different metabolic reasons. In both cases PET scans demonstrate a marked impairment of glucose utilisation in the several limbic regions, the hippocampal region, and the anterior cingulate cortex, while negative schizophrenic patients showed additional glucose uptake deficits in the thalamus, and frontal and parietal cortices (72,73). It is worthy of note, that this corresponds to the distribution of GLUT3 which is most abundant in the prefrontal cortex and moderately abundant in the parietal lobe, the hippocampal region, and the cerebellum. On the other hand, GLUT1 is most abundant in the basal ganglia and the thalamus (41). Positive schizophrenia is more responsive to the typical range of neuroleptics which target the D1 and D2 receptors in the basal ganglia, substantia nigra, ventral tegmental area, the striatal and mesolimbic sites (72,73). Equally, negative schizophrenia, in respect of which a leading symptom is relative hypofrontality (42), is more responsive to the atypical neuroleptics which target the D4 receptors (74,75) that markedly increase dopamine release in the prefrontal cortex (where GLUT3 is most highly expressed), the mesolimbic sites, and the striatum. Thus, negative schizophrenia is associated with decreased DAD4 activity, the DAD4 receptor being the specific target of the atypical neuroleptics through which dopamine release is increased in the prefrontal cortex, the mesolimbic sites and the striatum (76,77). Conversely, positive schizophrenia is associated with increased dopamine levels and the typical neuroleptics specifically target the DAD1 and DAD2 receptors by inactivating dopamine neurons in the substantia nigra and ventral tegmental areas (78) while simultaneously inducing dopamine release in the striatal and mesolimbic sites (76,77).

As mentioned previously, under normal conditions, diminished levels of dopamine will enhance prolactin secretion and activation of the PLC-PKC signal transduction pathway that activates the glucose transporters. Conversely, elevated levels of dopamine would stimulate the release of LHR, TRH, GnRH each of which activate the PLC/DAG/PKC pathway that also stimulates the activity of the glucose transporters. It is also not without interest that the D2 (79) and D4 (80) receptors are contained on the short arm of chromosome 11 together with tyrosinase, tyrosine and tryptophan hydroxylases, the Harvey-ras oncogene, and the insulin, IGF1 and IGF2 receptors (65). Thus, the respective location of the D2 and D4 receptors is consistent with the critical role that the catecholamines generally, and dopamine in particular, appear to play in glucose regulation and transport – a factor which is supported by an observed improvement in glucose uptake on PET scans following neuroleptic treatment (42).

Schizophrenia as a diabetic brain state

Thus far, it has been argued that dopamine appears to play a critical role in glucose regulation and transport and there is some scientific evidence to support this contention. Bhattacharya and Saraswati (81) studied the effects of insulin on brain monoamines during an alloxan-induced hyperglycaemic state. These researchers obtained conclusive evidence that insulin and insulin receptors, in the mammalian brain, act through neurotransmitter mediation (DA, NA, 5HT & ACh). During a hyperglycaemic state, brain concentrations of dopamine, serotonin, and noradrenaline were *elevated* in the midbrain-diencephalon (MD) and caudate nucleus (CN) but acetylcholine levels *decreased*. In the insulin-induced hypoglycaemic state, dopamine and noradrenaline levels *decreased*, while serotonin and acetylcholine levels *increased*. As an aside, these empirical observations may well explain the positive response of tardive dyskinesia to low doses of insulin (82). Since insulin decreases dopamine and increases acetylcholine levels, and tardive dyskinesia is thought to be associated with nigrostriatal dopamine overactivity and acetylcholine underactivity (83), insulin would have the effect of lowering dopamine and elevating acetylcholine activity. (In drug-induced parkinsonism nigrostriatal dopamine is thought to be underactive while ACh is overactive (83) and in Alzheimer's disease ACh levels are depleted in several brain regions (84)).

The findings of Bhattacharya and Saraswati are also supported by Gupta et al (85) who examined the effects of catecholamine metabolism in the frontal cortex of the rat brain during alloxan-induced hyperglycaemia and insulin-induced hypoglycaemia. They found that insulin-induced hypoglycaemia decreased dopamine activity while alloxan-induced hyperglycaemia increased dopamine activity. That dopamine and serotonin are elevated in the hyperglycaemic state and depressed in the hypoglycaemic state, is consistent with the findings of Linnoila et al (51) and Brown et al (86). Brown et al found a significantly higher incidence of violent suicidal behaviour in patients with low 5HIAA, a serotonin metabolite. Similarly, Linnoila et al later confirmed that, among criminal offenders, externally directed impulsive violent behaviour (including impulsive fire setting) and suicide by violent means, was negatively correlated with low 5HIAA, the NA metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), and hypoglycaemia. It was also found in this study that the incidence of aggressive, impulsive outbursts increased during transient hypoglycaemic episodes which was associated with elevated insulin outputs. In addition, the families of these hyperinsulinemic offenders confirmed an early onset of conduct disordered behaviour which included lying, stealing, abusive language, and alcohol abuse. In an effort to reverse the hypoglycaemic state, by increasing levels of serotonin, Linnoila et al administered ECT to genetically diabetic and genetically obese mice. They found that ECT improved glucose levels in the obese mice which parallels late onset noninsulin dependent diabetes mellitus (NIDDM) in humans.

Improved diabetic control with ECT was first reported by Fakhri et al (87) in 1979. This group administered ECT to 14 patients with diabetes, 8 of whom experienced complete remission of diabetic symptoms following one or two applications of ECT. All those who recovered had a diagnosis of NIDDM. Whilst this result could not be satisfactorily explained at the time, it is now known that ECT increases serotonin turnover, reduces hyperglycaemia (51); increases the activity of GTP-cyclohydrolase and tyrosine hydroxylase, and increases the levels of BH4 (48). Thus, to some extent, ECT parallels the action of lithium carbonate in that both improve mood control, ECT with respect to psychotic depression and lithium with respect to mood lability. The findings of Fakhri et al are consistent with those of Broderick and Jacoby (88) who examined central monoamine dysfunction in diabetes. They found that in chronically diabetic rats there was a significant inhibition of serotonin release in the striatum, while striatal dopamine was marginally increased. Conversely, the effect of hyperglycaemia on nondiabetic rats produced a 52% decrease of striatal dopamine release and a concomitant 304% increase in striatal serotonin release. It was suggested by these researchers that in an untreated diabetic state there would be progressive impairment of neurotransmitter release and that mood changes associated with the diabetic state may be related to impaired neurotransmitter availability.

That there is some association between mood states and blood glucose levels has been demonstrated by Gonder-Frederick et al (89) in relation to insulin-dependent diabetes mellitus (IDDM). These researchers found that low blood glucose was generally associated with negative mood states while high blood glucose was generally associated with positive mood states. These findings are congruent with those of Baxter et al (90) who used PET scans to compare the cerebral glucose metabolic rates between unipolar depressed, bipolar depressed, manic and normal controls. They found there was a global reduction in cerebral glucose metabolic rates in the bipolar depressed patients which proportionally increased as the patient switched to mania. Thus, in the frankly manic

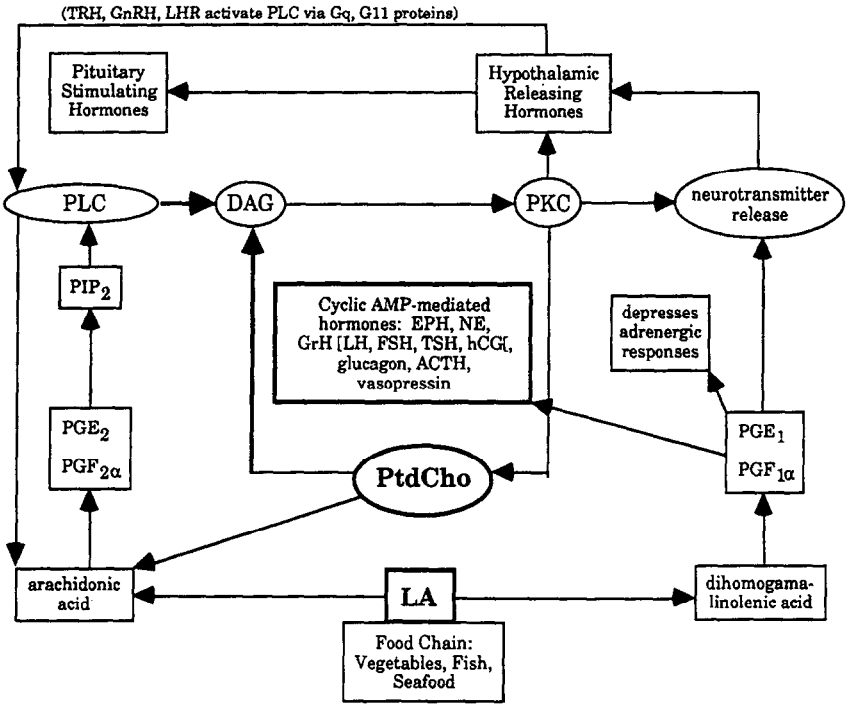

Fig. 3 Showing the interaction between essential fatty acids, prostaglandins, neurotransmission, and the neuroendocrine system. Abbreviations: (PLC) phospholipase C, (PKC) protein kinase C, (DAG) diacylglycerol, (GrH) glycoprotein hormones, (PtdCho) phosphotidylcholine, ($PGE_{1,2}$) ($PGF_{1,2\alpha}$) prostaglandins, (LA) linoleic acid, (PIP_2) phosphatidylinositol 4,5-bisphosphate. cAMP Mediated hormones: (EPH) epinephrine, (NE) norepinephrine. Glycoprotein hormones: (LH) lutineizing hormone, (FSH) follicle stimulating hormone, (TSH) thyrotropin stimulating hormone, (hCG) human chorionic gonadotrophin.

state they found a significant increase in frontal lobe blood flow. In this respect, Buchsbaum (42) notes some parallels in PET scan imaging between the bipolar depressed patients observed by Baxter et al (90) and the schizophrenic patients observed by himself in that both groups manifest persistent hypofrontality and a concomitant decrease in glucose uptake in the basal ganglia. These results have also been observed in unipolar depression (42) which seems to suggest that depression and negative schizophrenia share a continuum of liability in association with hypoglycaemia. This suggestion is consistent with the phenomena of post-psychotic depression which, in all probability, precedes schizophrenic decompensation rather than following it. On the other hand, PET scan data indicate that mania constitutes a discretely different metabolic state (90) and it may well be that mania and positive schizophrenia also share a continuum of liability in association with hyperglycaemia.

From PET scan data, it appears incontrovertible that the prefrontal cortex and the basal ganglia reflect impoverished glucose uptake during depressive and schizophrenic episodes. However, it was earlier mentioned that during hypoxic, hyperglycaemic, or hypoglycaemic states, the expression of GLUT1 is increased in the plasma membrane (32,33). Thus, in the hyperglycaemic state, an increased abundance of GLUT1 in the plasma membrane increases the susceptibility of the surrounding tissue to gain excess glucose (91). This is exactly what PET scans reflect in respect of positive schizophrenia (42) since the abnormal pattern of glucose activity corresponds with high abundance of GLUT1 in the basal ganglia and the thalamus, and moderate abundance of GLUT1 in the hippocampus and parietal cortices.

Thus, the positive response to neuroleptics in the basal ganglia region is now becoming more clear. Given that the expression of GLUT1 increases in the plasma membrane in response to hyper- and hypoglycaemia, it appears that neuroleptics facilitate an improvement in regional glucose metabolism. Conversely, the relative abundance of GLUT3 is not known to increase and, hence, an improvement in glucose metabolism in the prefrontal cortex, where it is exclusively expressed, is not observed. But hypoglycaemia is also associated with reduced dopamine

activity which neuroleptics aggravate by blocking the postsynaptic dopamine receptors. However, in the basal ganglia a short loop is activated to create a feedback mechanism, involving presynaptic dopamine receptors, in an attempt to overcome the DA receptor blockade together with a long loop that involves GABAergic and cholinergic neurons (57). On the other hand, in a hyperglycaemic metabolic state, consistent with mania and positive schizophrenia, there is an increased expression of GLUT1 in the plasma membrane which concomitantly increases the absorption of glucose into the cells, coupled with an increase in dopamine, serotonin, and noradrenaline activity. This would result in hypermetabolism in respect of GLUT1, particularly in the basal ganglia and thalamus, GLUT3 in the frontal cortex, and both GLUT1 and GLUT3 in the parietal lobe, hippocampus, and cerebellum.

Hypometabolism in these brain regions would result in a flattened or blunted affect, impaired cognition and movement disturbances (basal ganglia), and pain insensitivity (thalamus) [GLUT1 distribution]; poverty of ideas (frontal cortex) [GLUT3 distribution]; impaired visual, tactile, and/or auditory processing (parietal lobe); impaired memory, poor transfer of learning (hippocampus); and psychomotor retardation (cerebellum) (92,93) [GLUT1 and GLUT3 distribution] consistent with depression and/or negative schizophrenia. Conversely, hypermetabolism would result in an euphoric affect, heightened cognition, excessive movement (basal ganglia), and pain sensitivity (thalamus) [GLUT1]; flight of ideas [GLUT3]; visual, tactile, and auditory hallucinations (parietal lobe); confabulatory/delusional material (hippocampus); and ill-coordinated hyperactivity (cerebellum) (92,93) [GLUT1 and GLUT3] consistent with mania and/or positive schizophrenia.

In essence, the relative location of the respective glucose transporters largely determines the areas of the brain most liable to be affected by either hypometabolism or hypermetabolism, both states of which will involve a major disruption to the efficient functioning of the neurotransmitters in each of these identified regional areas. Thus, the intricate interplay between the glucose transporters and the neurotransmitters results in a diabetic brain state consistent with mental illness generally and schizophrenia in particular.

Conclusion

In this paper we have outlined the interaction between glucose regulation and transport, essential fatty acids and prostaglandins, neurotransmission, and the neuroendocrine system. In the course of this explication it has been argued that schizophrenia can be reconceived as a diabetic brain state. It has been postulated that both mania and positive schizophrenia are essentially hyperglycaemic brain states in which the surrounding tissue absorbs excessive glucose due to increased GLUT1 abundance. The hyperglycaemic state is accompanied by marked metabolic overactivity in some specific brain regions and marked metabolic underactivity in others. This regional variation appears to correspond to the respective regional abundance of GLUT1 and GLUT3, a factor supported by PET scan data. Conversely, it has been argued that negative schizophrenia and depression are essentially hypoglycaemic conditions in which hypometabolism appears to be most prominent in the prefrontal cor-

Table 2 Showing the common symptoms of schizophrenia and their anatomical correlates

	Hypometabolism Symptoms	Brain region	Hypermetabolism Symptoms
GLUT1	Flat/blunted affect		Euphoric affect
	Impaired cognition hypoactivity	Basal ganglia	Heightened cognition hyperactivity
	Pain insensitivity	Thalamus	Pain sensitivity
GLUT3	Poverty of ideas	Frontal cortex	Flight of ideas
GLUT1 & GLUT3	Impaired visual, tactile, and auditory processing	Parietal lobe	Visual, tactile, auditory hallucinations
	Impaired memory, poor transfer of learning	Hippocampus	Phantasies/delusions
	Psychomotor retardation	Cerebellum	Ill-coordinated hyperactivity

Adapted from (92).

tex. However, both the hypoglycaemic and hyperglycaemic states induce a massive disruption to neurotransmission and the PKC signal transduction pathway.

In addition, studies show that hypoglycaemia is associated with hypodopaminergia caused by low levels of BH4 and prostaglandins, due to p21ras remaining in its inactive GDP-bound form. Inactive ras.GDP causes insulin and IGF1 down-regulation which, in turn, causes a decrease in DAG levels, PKC activity and, ultimately, the regulation of glucose transporters. On the other hand, hyperglycaemia is associated with hyperdopaminergia which also induces a collapse of the PKC signal transduction pathway. This is because elevated levels of dopamine inhibit the dopamine withdrawal mechanism necessary for the stimulation of the prolactin, AA, PGE_2 and $PGF_{2\alpha}$ pathway, and the PLC, DAG, PKC pathway. Since PGE_2 and $PGF_{2\alpha}$ deactivates ras.GAP, any overexpression of dopamine will cause a simultaneous overexpression of GAP due to the absence of the deactivation process. This means that dopamine overexpression will result in p21ras remaining in its inactive GDP-bound form which will, concomitantly, cause a collapse of the PKC signal transduction pathway, glucose transporters, and neurotransmission initiated by BH4. Thus, both positive and negative schizophrenia can be likened to a metabolic time-bomb which was, in all probability, activated very early in life. Given the sequence of metabolic events outlined above, any hyperglycaemic brain state will, without external intervention, ultimately reverse to a hypoglycaemic state. On the other hand, without medical intervention, a hypoglycaemic brain state is more liable to lead to chronicity which is a common fate for many psychiatric patients.

It is our contention that 'cerebral diabetes' is a more apt description of psychotic conditions due to the fact that cerebral diabetes parallels peripheral diabetes in its cause and course. In peripheral diabetes, there is a fluctuation between hyperglycaemia and hypoglycaemia, accompanied by an alteration in mood, in response to variations in diet. Similarly, in cerebral diabetes fluctuations in glycaemic states and mood also occur. One possible external cause for these fluctuations is in response to variations in diet given that it has been definitively shown that schizophrenics have a linoleic acid deficiency. We have also argued that the brain regions most affected by mental illness correspond to the relative abundance of the glucose transporters. However, there is one important difference that obtains between peripheral and cerebral diabetes. In the hyperglycaemic state GLUT4, which specialises in insulin-sensitive tissues, is down-regulated in the plasma membrane which causes a decrease in total muscle glucose disposal. GLUT4 is the most abundant transporter in fat and muscle tissue and is responsible for almost all the insulin-stimulated transport of glucose. Conversely, GLUT1 is responsible for non-insulin-stimulated transport (94). Thus, because GLUT1 is a non-insulin-stimulated glucose transporter, the expression of which increases in the plasma membrane during hyperglycaemia, the surrounding tissues in the brain gain excess glucose during hyperglycaemia, and sustain a concomitant glucose loss during hypoglycaemia (91).

It has been postulated that the cause of peripheral diabetes is due to defective regulation of the glucose transporters (91). While all five glucose transporters are expressed in the periphery, only GLUT1 and GLUT3 appear in the brain. Although GLUT1 is present in fat and muscle tissue, GLUT4 is the most abundant, consequently, any dysregulation of GLUT1 could be compensated for by GLUT4. However, there are no equivalent compensatory mechanisms that could be invested in the brain. Similarly, although GLUT3 appears in low levels in several human tissues, it is most abundant in the neuronal cells. Accordingly, if dysregulation of GLUT3 occurs, the consequences will be most marked in the brain. Furthermore, if peripheral diabetes is caused by the dysregulation of a specific glucose transporter, with GLUT4 being the most likely candidate, this explains how a person could be diabetic centrally and yet not be diabetic peripherally, since the respective glucose transporters involved are different in each case. It also explains the metabolic difference between the brain and periphery in response to hyperglycaemia since the respective glucose transporters behave differently in each case.

With respect to 'cerebral diabetes', there are three obvious points of intervention: (i) the elevation of BH4 levels which can already be achieved with ECT and lithium carbonate; (ii) the manipulation of insulin which has already proved an effective intervention in previous decades; and (iii) dietary control by increasing the intake of linoleic acid which will increase DGLA and AA levels and ultimately improve glucose transporter activity. A diet that enhances LA intake could also be supplemented by EFA drugs (55). However, whilst BH4 levels can be improved with ECT and lithium (47,95), oral supplements of BH4 have been given to infantile autistic patients with good effect (96,97) and it has been suggested as a possible therapeutic approach in the treatment of Alzheimer's disease (46). Finally, given improved peripheral diabetic control can also be achieved with ECT, the parallels between mental illness and diabetes are be-

coming increasingly apparent and reconceiving mental illness as 'cerebral diabetes' ought, ultimately, to improve the treatment outcome.

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References

1. Laqueur HP. Insulin coma therapy. In: Berger PA, Brodie H eds. American Handbook of Psychiatry. 2nd edn. Vol. 5. New York: Basic Books, 1986: 526-528.
2. Laqueur HP, LaBurt HA. Coma therapy with multiple insulin doses. J Neuropsychiatry 1960; 5: 135-147.
3. Bennett IF. Hormonal and other blood changes occurring during insulin hypoglycaemia treatment. In: Rinkel M, Himwich HE eds. Insulin Treatment in Psychiatry. London: Peter Owen Ltd., 1960: 45-84.
4. Himwich WA. Biochemical changes in the brain occurring during insulin hypoglycaemia. In: Rinkel M, Himwich HE, eds. Insulin Treatment in Psychiatry. London: Peter Owen Ltd., 1960: 85-99.
5. Dussik KT. The place of Sakel's insulin coma therapy in an active treatment unit of today. In: Rinkel M, Himwich HE, eds. Insulin Treatment in Psychiatry. London: Peter Owen Ltd., 1960: 316-331.
6. Burgering BMTh, Medema RH, Maassen JA et al. Insulin stimulation of gene expression mediated by p21ras activation. EMBO J 1991; 10: 1103-1109.
7. Boulton AA. The tyramine: functionally significant biogenic amines or metabolic accidents? Life Sci 1978; 23: 659–672.
8. Newman JC, Holden RJ. The 'cerebral diabetes' paradigm for unipolar depression. Med Hypotheses 1993; 41: 391-408.
9. Ohue T, Koshimura K, Lee K, Watanabe Y, Miwa S. A novel action of 6*R*-L-*erythro*-5,6,7,8,-tetrahydrobiopterin, a cofactor for hydrolases of phenalalanine, tyrosine and tryptophan: enhancement of acetylcholine release in vivo in the rat hippocampus. Neurosci Lett 1991; 128: 93-96.
10. Mataga N, Imamura K, Watanabe Y. 6R-tetrahydrobiopterin perfusion enhances dopamine, serotonin, and GLUtamate outputs in dialysate from rat striatum and frontal cortex. Brain Res 1991; 551: 64-71
11. Butt WR. Prostaglandins. In: Butt WR ed. Hormone Chemistry. 2nd edn. Chicester: Ellis Horwood Ltd., 1976: 243-261.
12. Medema RH, Burgering BMTh, Bos JL. Insulin-induced p21ras activation does not require protein kinase C, but a protein sensitive to phenylarsine oxide. Journal Biol Chem 1991; 266: 21186-21189.
13. Yu B, Standaert M, Arnold T et al. Effects of insulin on diacylglycerol/protein kinase-C signalling and glucose transport in rat skeletal muscles *in vivo* and *in vitro*. Endocrinology 1992; 130: 3345-3355.
14. Tranque PA, Calle R, Naftolin F, Robbins R. Involvement of protein kinase-C in the mitogenic effect of insulin-like growth factor-I on rat astrocytes. Endocrinology 1992; 131: 1948-1954.
15. Nori M, L'Allemain G, Weber MJ. Regulation of tetradecanoyl phorbol acetate-induced responses in NIH 3T3 cells by GAP, the GTPase-activating protein associated with p21$^{c\text{-}ras}$. Mol Cell Biol 1992; 12: 936-945.
16. Tsai MH, Yu CL, Wei FS, Stacey DW. The effect of GTPase activating protein upon *Ras* is inhibited by mitogenically responsive lipids. Science 1989; 243: 322-326.
17. Pronk GJ, Medema RH, Burgering BMTh, Clark R, McCormick F, Bos JL. Interaction between the p21ras GTPase activating protein and the insulin receptor. J Biol Chem 1992; 267: 24058-24063.
18. Hatakeyama K, Harada T, Kagamiyama H. IMP dehydrogenase inhibitors reduce intracellular tetrahydrobiopterin levels through reduction of intracellular GTP levels. Indications of the regulation of GTP cyclohydrolase I activity by restriction of GTP availability. J Biol Chem 1992; 267: 20734-20739.
19. de Vries-Smits AMM, Burgering BMTh, Leevers SJ, Marshall CJ, Bos JL. Involvement of p21^{ras} in activation of extracellular signal-regulated kinase 2. Nature 1992; 357: 602-604.
20. Medema RH, Wubbolts R, Bos JL. Two dominant inhibitory mutants of p21^{ras} interfere with insulin-induced gene expression. Mol Cell Biol 1991; 11: 5963-5967.
21. Polakis P, McCormick F. Interactions between p21^{ras} proteins and their GTPase activating proteins. Cancer Surv 1992; 12: 25-42.
22. Nakafuku M, Satoh T, Kaziro Y. Differentiation factors, including nerve growth factor, fibroblast growth factor, and interleukin-6, induce an accumulation of an active ras.GTP complex in rat pheochromocytoma PC12 cells. J Biol Chem 1992; 2647: 19448-19454.
23. Porras A, Nebreda AR, Benito M, Santos E. Activation of Ras by insulin in 3T3 L1 cells does not involve GTPase-activating protein phosphorylation. J Biol Chem 1992; 267: 21124-21131.
24. Kozma L, Baltensperger K, Klarlund J, Porras A, Santos E, Czech MP. The Ras signaling pathway mimics insulin action on glucose transporter translocation. Proc Natl Acad Sci 1993; 90: 4460-4464.
25. Sjolander A, Lapetina EG. Agonist-induced association of the p21ras GTPase-activating protein with phosphatidylinositol 3-kinase. Biochem Biophys Res Commun 1992; 189: 1503-1508.
26. Wetsel WC, Eraly SA, Whyte DB, Mellon PL. Regulation of gonadotrophin-releasing hormone by protein kinase A and -C in immortalized hypothalamic neurons. Endocrinology 1993; 132: 2360-2370.
27. Waters SB, Conn PM. Maintenance of gonadotrophin-releasing hormone (GnRH)-stimulated luteinizing hormone release despite desentitization of GnRH-stimulated cytosolic calcium responses. Endocrinology 1992; 130: 2091-2100.
28. Hu SB, Tannahill LA, Biswas S, Lightman SL. Release of corticotrophin-releasing factor 41, arginine vasopressin and oxytocin from rat fetal hypothalamic cells in culture: response to activation of intracellular second messengers and to corticosteroids. J Endocrinol 1992; 132: 57-65.
29. Arakawa M, Mizoguchi A, Masutani M, Kawakita N, Ide C. Ultrastructural localization of protein kinase C beta-subspecies in the axon terminal of rat neuromuscular junction. Neurosci Res 1993; 16: 125-130.
30. Robinson PJ. The role of protein kinase C and its neuronal substrates dephosin, B-50, and MARCKS in neurotransmitter release. Mol Neurobiol 1991; 5: 87-130.
31. Lienhard GE, Slot JW, James DE, Mueckler MM. How cells absorb glucose. Sci Am 1992; 266: 34-39.
32. Dimitrakoudis D, Ramlal T, Rastogi S, Vranic M, Klip A. Glycaemia regulates the glucose transporter number in the plasma membrane of rat skeletal muscle. Biochem J 1992; 284: 284-348.
33. Hundal HS, Ramlal T, Reyes R, Leiter LA, Klip A. Cellular

mechanism of metformin action involves glucose transporter translocation from an intracellular pool to the plasma membrane in L6 muscle cells. Endocrinology 1992; 131: 1165-1173.
34. Bashan N, Burdett E, Hundal HS, Klip A. Regulation of glucose transport and GLUT1 glucose transporter expression by O^2 in muscle cells in culture. Am J Physiol 262 (Cell Physiology 31) 1992; C682-C690.
35. Boado RJ, Pardridge WM. Glucose deprivation causes posttranscriptional enhancement of brain capillary endothelial glucose transporter gene expression via GLUT1 mRNA stabilization. J Neurochem 1993; 60: 2290-2296.
36. Rapoport MJ, Lazarus AH, Jaaramillo A, Speck E, Delovitch TL. Thymic T cell anery in autoimmune nonobese diabetic mice is mediated by deficient T cell receptor regulation of the pathway of p21ras activation. J Exp Med 1993; 177: 1221-1226.
37. Klip A, Marette A. Acute and chronic signals controlling glucose transport in skeletal muscle. J Cell Biol 1992; 48: 51-60.
38. Gherzi R, Melioli G, de Luca M. 'HepG2/erythroid/brain' type glucose transporter (GLUT1) is highly expressed in human epidermis: keratinocyte differentiation affects GLUT1 levels in reconstituted epidermis. J Cell Physiol 1992; 150: 463-474.
39. Saltis J, Habberfield AD, Egan JJ, Londos C, Simpson IA, Cushman SW. Role of protein kinase C in the regulation of glucose transport in the rat adipose cell. J Biol Chem 1991; 266: 261-267.
40. Longo N, Griffin LD, Langley SD, Elsas LJ. Glucose transport by cultured human fibroblasts: regulation by phorbol esters and insulin. Biochim Biophys Acta 1992; 1104: 24-30.
41. Yano H, Seino Y, Inagaki N et al. Tissue distribution and species difference of the brain type glucose transporter (GLUT3). Biochem Biophys Res Commun 1991; 174: 470-477.
42. Buchsbaum JS, Wu J, DeLisi LE et al. Frontal cortex and basal ganglia metabolic rates assessed by positron emission tomography with (^{18}F) 2-Deoxyglucose in affective illness. J Affect Disord 1986; 10: 137-152.
43. Egeland JA, Gerhard DS, Pauls DL et al. Bipolar affective disorders linked to DNA markers on chromosome 11. Nature 1987; 325: 783-787.
44. Owerbach D, Gunn S, Gabbay KH. Multigenic basis for Type I Diabetes: association of HRAS1 polymorphism with HLA-DR3, DQw2/DR4, DQw8. Diabetes 1990; 39: 1504-1509.
45. Meltzer HY. Beyond serotonin. J Clin Psychiatry 1991; 52 [5, suppl]: 58-62.
46. Aziz AA, Leeming RJ, Blair JA. Tetrahydrobiopterin metabolism in senile dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 1983; 46: 410-413.
47. Anderson DN, Abou-Saleh MT, Collins J et al. Pterin metabolism in depression: an extension of the amine hypothesis and possible marker of response to ECT. Psychol Med 1992; 22: 863-869.
48. Hossain MA, Masserano JM, Weiner N. Effects of electroconvulsive shock on tetrahydrobiopterin and GTP-cyclohydrolase activity in the brain and adrenal gland of the rat. J Neurochem 1992; 59: 2237-2243.
49. Hossain MA, Masserano JM, Weiner N. Comparative effects of electroconvulsive shock and haloperidol on in vivo tyrosine hydroxylation and tetrahydrobiopterin in the brain of rats with 6-hydroxydopamine lesions. Brain Res 1992; 598: 121-126.
50. Hamon CG, Cutler P, Blair JA. Tetrahydrobiopterin metabolism in *streptozotocin* induced diabetic state in rats. Clin Chim Acta 1989; 181: 249-254.
51. Linnoila VMI, Virkkunen M. Aggression, suicidality, and serotonin. J Clin Psychiatry 1992; 53: 10[suppl], 46-51.
52. Hsieh KP, Martin TF. Thyrotropin-releasing hormone and gonadotropin-releasing hormone receptors activate phospholipase C by coupling to the guanosine triphosphate-binding proteins Gq and G11. Mol Endocrinol 1992; 6: 1673-1681.
53. Gudermann T, Birnbaumer M, Birnbaumer L. Evidence for dual coupling of the murine luteinizing hormone receptor to adenylyl cyclase and phosphoinositide breakdown and Ca2+ mobilization. Studies with cloned murine luteinizing hormone receptor expressed in L cells. J Biol Chem 1992; 267: 4479-4488.
54. Adamo M, Raizada MK, LeRoith D. Insulin and insulin-like growth factor receptors in the nervous system. Mol Neurobiol 1989; 3: 71-100.
55. Horrobin DF. Essential fatty acids, prostaglandins and schizophrenia. In: CN Stefanis et al, eds. Psychiatry: A World Perspective – Volume 2. Amsterdam: Elsevier Science Publishers B.V., 1990: 140–144.
56. Martinez de la Escalera G, Weiner RI. Dissociation of dopamine from its receptor as a signal in the pleiotropic hypothalamic regulation of prolactin secretion. Endocrinol Review 1992; 13: 241-255.
57. Nelson TJ, Alkon DL. GTP-binding proteins and potassium channels involved in synaptic plasticity and learning. Mol Neurobiol 1992; 5: 315-327.
58. Wyatt RJ, Kirch DG, DeLisi LN. Schizophrenia: biochemical, endocrine, and immunological studies. In: Kaplan HI, Sadock BJ eds. Comprehensive Textbook of Psychiatry/V. 5th edn. Baltimore: Williams and Wilkin, 1989: 717-732.
59. Davidson M, Losonczy MF, Davis KL. Biological hypotheses of schizophrenia. In: Berger PA, Brodie HKH eds. American Handbook of Psychiatry, Vol 8, 2nd edn. New York: Basic Books, 1986: 429-465.
60. Lohr JB, Flynn K. Smoking and schizophrenia. Schizophr Res 1992; 8: 93-102.
61. Sandyk R, Kay SR. Tobacco addiction as a marker of age at onset of schizophrenia. Intern J Neuroscience 1991; 57: 259-262.
62. Yassa R, Samarthji L, Korpassy A, Ally J. Nicotine exposure and tardive dyskinesia. Biol Psychiatry 1987; 22: 67-72.
63. Binder RL, Kazamatsuri H, Nishimura T, McNiel DE. Smoking and tardive dyskinesia. Biol Psychiatry 1987; 22: 1280-1282.
64. Naoi M, Hosoda S, Ota M, Takahashi T, Nagatsu T. Inhibition of tryptophan hydrolase by food-derived carcinogenic heterocyclic amines, 3-amino-1-methyl-*5H*-pyrido[4,3-*b*]indole and 3-amino-1,4-dimethyl-$_{5H}$-pyrido[4,3-*b*]indole. Biochem Pharmacol 1991; 41: 199-203.
65. Holden RJ, Mooney PA. Schizophrenia: An extended etiological explanation. Med Hypotheses; 1994 (in press).
66. McCann SM, Ojeda SR. The anterior pituitary and hypothalamus. In: Griffin JE, Ojeda SR eds. Textbook of Endocrine Physiology, 2nd edn. Oxford: Oxford University Press, 1992: 75-105.
67. Horrobin DF. The relationship between schizophrenia and essential fatty acid and eicosanoid metabolism. Prostaglandins Leukot Essent Fatty Acids 1992; 46: 71-77.
68. Glen AIM, Glen EMT, Horrobin DF et al. A red cell membrane abnormality in a sub-group of schizophrenic patients: Evidence for two diseases. Schizophr Res, 1993 (in press).
69. Sandyk R, Kay SR. Drug-induced Parkinsonism: Relationship to age at onset of schizophrenia. Funct Neurol 1991; 6: 151-157.
70. Price BD, Morris JDH, Marshall CJ, Hall A. Stimulation of phosphatidylcholine hydrolysis, diacylglycerol release, and arachidonic acid production by oncogenic ras is a consequence of protein kinase C activation. J Biol Chem 1989; 264: 16638-

16643.
71. Deniker P. The neuroleptics: a historical survey. Acta Psychiatr Scand 1990; 82 [Suppl. 358]: 83-87.
72. Tamminga CA, Burrows GH, Chase TN, Alphs LD, Thaker GK. Dopamine neuronal tracts in schizophrenia: their pharmacology and in vivo glucose metabolism. Ann NY Acad Sci 1988; 537: 443-450.
73. Tamminga CA, Thaker GK, Buchanan R et al. Limbic system abnormalities identified in schizophrenia using positron emission tomography with fluorodeoxyglucose and neocortical alterations with deficit syndrome. Arch Gen Psychiatry 1992; 49: 522-530.
74. Seeman P. Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 1992; 7: 261-284.
75. Goldstein M, Deutch AY. Dopaminergic mechanisms in the pathogenesis of schizophrenia. FASEB J 1992; 6: 2413-2421.
76. Moghaddam B, Bunney BS. Acute effect of typical and atypical antipsychotic drugs on the release of dopamine from prefrontal cortex, nucleus accumbens, and striatum of the rat: an in vivo microdialysis study. J Neurochem 1990; 54: 1755-1760.
77. Moghaddam B, Bunney BS. Utilization of microdialysis for assessing the release of mesotelencephalic dopamine following clozapine and other antipsychotic drugs. Prog Neuro-Psychopharmacol Biol Psychiatry 1990; 14: S51-S57.
78. Bunney BS, Sesack SR, Silva NL. Midbrain dopaminergic systems: neurophysiology and electrophysiological pharmacology. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York: Raven, 1987: 113-126.
79. Mendlewicz J, Sevy S, Mendelbaum K. Minireview: Molecular genetics in affective illness. Life Science 1993; 52: 231-242.
80. Gelernter J, Kennedy JL, van Tol HH, Civelli O, Kidd KK. The D4 dopamine receptor (DRD4) maps to distal 11p close to HRAS. Genomics 1992; 13: 208-210.
81. Bhattacharya SK, Saraswati M. Effect of intracerebroventricularly administered insulin on brain monoamines and acetylcholine in euglycaemic and alloxan-induced hyperglycaemic rats. Indian J Exp Biol 1991; 29: 1095-1100.
82. Mouret J, Khomais M, Lemoine P, Sebert P. Low doses of insulin as a treatment of tardive dyskinesia: conjuncture or conjecture? Eur Neurol 1991; 31: 199-203.
83. Jeste DV, Iager AC, Wyatt RJ. The biology and experimental treatment of tardive dyskinesia and other related movement disorders. In: Berger PA, Brodie HKH, eds. American Handbook of Psychiatry, 2nd edn. New York: Basic Books, 1986: 536-580.
84. Nemeroff CB, Bissette G. Neuropeptides in psychiatric disorders. In: Berger PA, Brodie HKH, eds. American Handbook of Psychiatry, 2nd edn. New York: Basic Books, 1986: 64-110.
85. Gupta G Azam M, Baquer NZ. Effect of experimental diabetes on the catecholamine metabolism in rat brain. J Neurochem 1992; 58: 95-100.
86. Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry Res 1979; 1: 131-139.
87. Fakhri O, Fadhli AA, el Rawi RM. Effect of electroconvulsive therapy on diabetes mellitus. Lancet 1980; October 11: 775-777.
88. Broderick PA, Jacoby JH. Central monoamine dysfunction in diabetes: psychotherapeutic implications: electroanalysis by voltammetry. Acts Physiol Pharmacol Latinoam 1989; 39: 211-225.
89. Gonder-Frederick LA, Cox DJ, Bobbitt SA, Pennebaker JW. Mood changes associated with blood glucose fluctuations in insulin-dependent diabetes mellitus. Health Psychol 1989; 8: 45-59.
90. Baxter Jr. LR, Phelphs MD, Mazzoitta JC. Cerebral metabolic rates for glucose in mood disorders: studies with positron emission tomography and fluorodeoxyglucose F 18. Arch Gen Psychiatry 1985; 42: 441-447.
91. Dimitrakoudis D, Vranic M, Klip A. Effects of hyperglycaemia on glucose transporters of the muscle: use of the renal glucose reabsorption inhibitor phlorizin to control glycaemia. J Am Soc Nephrol 1992; 3: 1078-1091.
92. Kaplan HI, Sadock BJ. The brain and behaviour. In: Synopsis of Psychiatry: Behavioural Sciences, Clinical Psychiatry, 6th edn. Baltimore, Williams and Wilkin, 1991: 63-103.
93. Horvath TB. The psychological presentations of somatic disorders. In: Berger PA, Brodie HKH, eds. American Handbook of Psychiatry, 2nd edn. New York: Basic Books, 1986: 900-943.
94. Mueckler M. The molecular biology of glucose transport: relevance to insulin resistance and non-insulin-dependent diabetes mellitus. J Diabet Complications 1993; 7: 130-141.
95. Coppen A, Swade C, Jones SA, Armstrong RA, Blair JA, Leeming RJ. Depression and tetrahydrobiopterin: the folate connection. J Affect Disord 1989; 16: 103-107.
96. Eto I, Bandy M, Butterworth Jr CE. Plasma and urinary levels of biopterin, neopterin, and related pterins and plasma levels of folate in infantile autism. J Autism Dev Disord 1992; 22: 295-308.
97. Naruse H, Hayashi T, Takesada M, Nakane A, Yamazaki K. Metabolic changes in aromatic amino acids and monoamines in infantile autism and development of new treatment related to the finding. No To Hattatsu 1989; 21: 181-189.