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Review Article

The Immune and Metabolic Factors of Schizophrenia

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Abstract

Schizophrenia is a neurodevelopmental illness where involvement of both environmental and genetic triggers is proposed. While a neuronal cell-autonomous view of schizophrenia has been suggested, increasing evidence is pointing beyond intrinsic neuronal dysfunction to help explain reasons for this illness. In particular, the role of immune and metabolic systems, unifying the behavioral and physical factors of schizophrenia is being debated. In this model of disease, abnormal function and communication between cells of the immune, metabolic and/or central nervous systems, in part, play a role. Particular support for this hypothesis comes from reports showing altered levels of pro-inflammatory cytokines in patients with schizophrenia. Such molecules have been suggested to originate from dysfunctional immune cells, adipocytes and/or glial cells. In this review, we discuss how metabolic and immune dysfunction may help explain and unify the genetic and environmental hypothesis of schizophrenia. We also discuss how aberrant release of inflammatory markers from immune cells, adipocytes and glial cells could contribute to schizophrenia. We conclude, by asking if there are blood-borne signalling molecules released by these cells which still require discovery and could further explain this illness.

Introduction

Schizophrenia occurs in late adolescence or early adulthood with a median incidence of 15 per 100,000 person years and rate ratio somewhat higher in males[1,2]. The symptoms of schizophrenia include positive symptoms that embody classic psychosis, such as sensory hallucinations, delusions or disorganized thinking and negative symptoms include lack of emotional response (blunted affect), unprompted speech (alogia) and motivation (avolition). Patients with schizophrenia also experience cognitive dysfunction, impaired attention and executive function; emotional and behavioural difficulties with intellectual and language alterations, as well as subtle motor delays [3]. While some patients may only experience one psychotic episode, many will follow a relapsing course over their lifetime [4]. The lifespan of patients with schizophrenia is shortened by up to 25 years, the cause of which likely includes suicide, lifestyle risk factors, cardiovascular disease and obesity amongst others [5,6]. Clinical diagnosis of schizophrenia is made using criteria specified in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) and International Classification of Diseases-10 (ICD-10). Structural brain abnormalities occur in schizophrenia but are not sensitive enough (approximately 40-50% patients) or specific enough (seen in approximately 10% of normal controls) to be of diagnostic benefit [7]. At present, there is also no evidence-based biomarker to diagnose schizophrenia currently in practice and the biological entity of schizophrenia is based on patient introspection and clinical observation. Moreover, while

pharmacological treatments can help manage positive symptoms, there are currently no drugs that are effective in the treatment of negative symptoms in patients with schizophrenia [8]. In schizophrenia the estimated risk in monozygotic twins is higher than in dizygotic twins and if one parent has schizophrenia the lifetime risk for each child is lower than if both parents have schizophrenia [9]. Genome wide association studies (GWAS) have identified common variants and propose interplay between numerous genes, which likely serve to lower the threshold for developing the disorder [9]. Genetic variations associated with schizophrenia have supported a role for altered brain function, neurodevelopment and neuroplasticity. Moreover, these networks of genes have been linked to abnormal synaptic function and to altered dopamine or glutamate neurotransmission [10,11]. Of particular interest, are emerging data from GWAS now showing association of genes with metabolic and immune functions, please see references within [9,12,13]. Here, we discuss if these non-neuronal mechanisms may explain further and help unify the genetic and environmental hypothesis of schizophrenia.

2. Synaptic Abnormalities in Schizophrenia

It is now accepted that schizophrenia has a neurodevelopmental origin with involvement from both gene and environment effects [14]. In schizophrenia, normal brain development is likely impaired long before the first symptoms of psychosis, where both macro- and micro-anatomical structural abnormalities have been reported. At the macro-anatomical level an overall reduction in whole brain volume, with a decrease in grey matter, alteration of white matter tracts and an increase in ventricular volume is found in this illness[15]. At the micro-anatomical level abnormal synaptic pruning, in particular hyperpruning, of collateral axons in the prefrontal cortex may predispose to the clinical manifestation of schizophrenia. These structural abnormalities have led to suggestions of neurodevelopmental (and perhaps even neurodegenerative) processes as causes for this illness[16]. The concept of abnormal synaptic function either due to abnormal synaptic pruning or altered neurotransmitter levels has been the mainstay mechanism thought to underlie schizophrenia. Current treatment options are also primarily based on the hypothesis that aberrant neurotransmitter signalling occurs in schizophrenia, where increased dopaminergic, increased serotonergic, and hypoactive glutamatergic signalling is proposed, please see references within[17]. In this paradigm, activation of dopamine receptors by amphetamine and activation of 5-HT receptors by lysergic acid diethylamide (LSD) induce psychosis-like symptoms and hallucinogenic effects, respectively[18]. Moreover, inhibition of NMDA glutamate receptors by phencyclidine (PCP) and ketamine, as well as autoantibodies to NMDA receptors reproduce the symptomatic, neurocognitive and neurochemical aspects of schizophrenia[19]. Accordingly, the drugs used in patients with schizophrenia work primarily as antagonists to D2 dopamine receptors and 5-HT2A receptor. In addition, dopamine partial agonists, such as aripiprazole, have also emerged as antipsychotic treatments [20]. More recently, the role of complement is synaptic pruning has also been suggested, potentially linking abnormal immune function with abnormal neurodevelopment in schizophrenia [21,22].

3. Metabolic Syndrome and Schizophrenia

Metabolic syndrome is observed in schizophrenia, with some suggesting it's prevalence to be higher in this illness compared to the general population[23,24]. Metabolic syndrome is diagnosed primarily by central adiposity, due to obesity and is associated with elevated triglycerides, glucose and blood pressure, with decreased HDL cholesterol levels. This syndrome is linked to diseases such as type 2 diabetes and cardiovascular disease[23]. Insulin resistanceappears to be a common predecessor to metabolic syndrome, where unresponsiveness to insulin leads to increased blood glucose and free fatty acid uptake in the liver (Figure 1) [23]. In schizophrenia there is increased prevalence of type 2 diabetes mellitus and coronary heart disease, as well as decreased HDL cholesterol levels [25-27]. This increased risk impacts on the physical health of patients reflected by premature mortality [5].The aetiology of metabolic syndrome in schizophrenia remains unclear and is likely multifactorial, involving effects of life stress, unhealthy lifestyle, as well as poor diet characterised by a high intake of saturated fat and decreased fibre [28]. Medication may also increase the risk of metabolic syndrome, which is related to a drug-induced weight gain observed with some atypical antipsychotics, such as clozapine[29], although studies have also reported abnormal glucose metabolism in first-episode schizophrenia [27]. At the cellular level, insulin resistance and increased free fatty uptake is associated with mitochondrial overload and oxidative stress and inflammation [30,31] (Figure 1). In this state, adipose tissue cells (such as macrophages and adipocytes) can release abnormal amounts of pro-inflammatory cytokines [32]. In patients with schizophrenia, there are also associations between white blood cell counts, C-reactive protein, and the metabolic syndrome [33-35]. Overall, therefore, it appears that inflammatory events in metabolic syndrome and schizophrenia may, in part, sharecommon mechanistic underpinnings[36]. A paradox that remains, however, is that clozapine induces prominent metabolic syndrome while still proving effective in the treatment of refractory schizophrenia. These apparent anomalous findings raise discussion as to whether metabolic syndrome, while negatively impacting upon physical health, may beneficially attenuate psychotic symptoms in schizophrenia. Such a paradigm may help explain the efficacy of atypical antipsychotics, such as

clozapine, in schizophrenia.

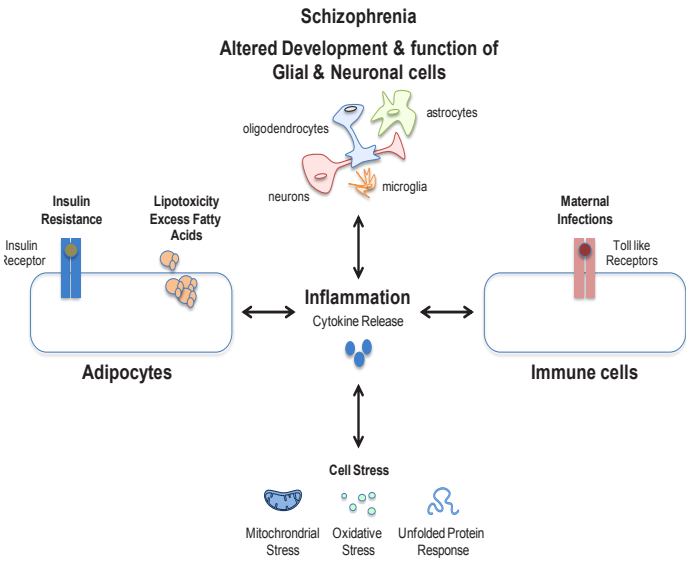

Figure 1. Environmental triggers of schizophrenia. The diagram shows cross-talk between cells of adipose, immune and brain tissues. A dysfunction in this communication may play a role in development and maintance of ill health in schizophrenia. Depicted is how insulin resistance and lipotoxicity, and maternal infections alter adipocyte and immune cell function, respectively. Such triggers induce cell stress (mitochondrial stress, oxidative stress and unfolded protein response stress) and promote release of pro-inflammatory cytokines from these cells.

4. Altered Immune Function in Schizophrenia

A developmental model of neuroinflammation has been proposed as a mechanism underlying schizophrenia [37-39]. Here, the onset of schizophrenia may occur inindividuals who have a genetic predisposition as an initial triggerand also experience an inflammatory insult at an early stage in life (Figure 2). Prenatal infections and malnutrition in the first and second trimesters are hypothesized to detrimentally alter the developing immune system, causing downstream effects that may ultimately affect brain maturation and prime an individual for developing schizophrenia[40-42]. Such in-uteroinsults may involve the production of pro-inflammatory cytokines, oxidative stress and the priming of microglia and astrocytes, which ultimately alter neuronal function in the long-term[37,43]. An increased incidence of schizophrenia has also been associated in first and second-generation migrants, where early life stress may play a role[44]. Excessive stress or substanceuse(e.g. cannabis) occurring in adolescence or early adulthood have also been suggested as 'second hits' that may induce schizophrenia (Figure 2)[18]. Overall these studies point to a role for altered immune response at an early age that may predispose individuals to the onset of schizophrenia. Supporting a neuroinflammation hypothesis for schizophreniaare results from small sampleclinical studies demonstrating beneficial effects of non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib and aspirin as adjuvants in schizophrenia, please see references within[45]. Novel inflammatory compounds such as fingolimod, a sphingosine 1 phosphate receptor agonist [46] are also now being tested in schizophrenia (NCT01779700), highlighting the immune system as a potential novel drug target for this illness.

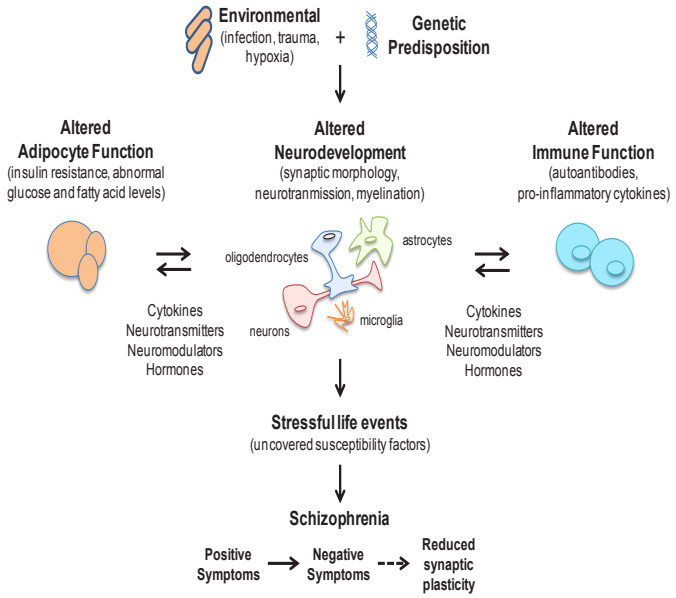

Figure 2. The hypothetical neuroinflamation hypothesis of schizophrenia. The diagram suggests that (i) initial genetic and/or environmental impacts, (ii) followed by altered brain neurodevelopment and (iii) subsequent stress (life, drug abuse, or other) faced in adolescence or early adulthood contribute, in a concerted manner, to the onset and development of schizophrenia. Notably, each of these events likely alters immune function, which is hypothesized to play a role in this illness.

5. Aberrant Cytokine Signalling in Schizophrenia

The multi-directional communication between immune, metabolic and central nervous systems is supported by the release of signalling molecules and commonly expressed receptors for cytokines, hormones and neurotransmitters on these various cell types [47,48]. This carefully controlled cellular communication may conceivably be deregulated by both genetic variations and environmental triggers, which in turn cancoalesce to play a concerted role in schizophrenia (Figure 2) [49]. There is evidence to support the idea that cells of the immune, metabolic and central nervous systems (e.g. immune cells, adipocytes, glial cells and others) can share and

communicate via common messengers and that disruption in such signalling occurs in schizophrenia. In particular, a 'cytokine hypothesis' for schizophrenia has been proposed, where studies have reported an association between altered cytokine levels andschizophrenia, please see Table 1 [34,50-53]. While many of these studies have been contradictory, taken together, this body of literature suggests that altered secretion patterns of cytokines may occur in schizophrenia. These findings have been suggested to potentially link altered immune cell response, aberrant adipocyte function and abnormal glial cell activityin schizophrenia (Figure 2). Altered communication between cells of the immune, metabolic and central nervous systems may not only occur via the mismanagement of cytokines, but perhaps also by a range of other signalling molecules. Such factors include autoantibodies, free fatty acids, environmental toxins and many more, potentially yet undiscovered, which could originate from inside or outside the brain and induce psychosis.

schizophrenia where data from GWAS have identified potential neuronal targets. Notably, however, alternative explanations to neuronal cell-autonomous mechanisms for schizophrenia are now being suggested. Amongst these, abnormalities in the immune and metabolic systems have been associated with schizophrenia. In this model of disease, cytokines (as well as neurotransmitters, hormones, neurohormones, growth factors, and even auto-antibodies) are proposed to serve as messengers between immune, metabolic and central nervous systems, where altered circulating levels occur in schizophrenia. To date, however, none of these molecules have been described as a sole cause of schizophrenia or as robust diagnostic biomarkers for this disorder. Thus, a further understanding of the pathways that are disrupted in this illness may to develop a multi-factorial and multi-cellular mechanism for this illness that may in turn identify novel drug targets.

		S100B	IL-1	IL-2	IL-6	IL-8	TNF-α	IL-17	IFN-γ	IL-23	IL-4	IL-10
Schizophrenia	↑	4, 33, 91, 117, 119	1, 2, 18, 26, 41, 46, 48	23-25, 29-31, 70	1,2,23,27,28,35-39 ,42,45-46,116	1, 2, 48	2, 18, 26, 46, 48	48	50, 51	48	118	55
	↔		25, 34, 40, 43, 44, 47, 69, 79	20-22, 44, 79	19, 32, 34, 38, 40, 41, 43, 48		32, 34, 52-54, 19		10, 11, 18, 19, 21, 49, 118		19	19, 118
	↓		20	19, 26				3				
Schizophrenia *(in vitro studies)*	↑	120	71	66-68	115				66, 78			
	↔		25, 59	69	20, 25		54					56, 66, 67
	↓			22,25,56-65					56, 69, 72-77			
Metabolic syndrome	↑	92, 93	5, 80, 81, 83, 84, 85, 87	88	5, 6, 7, 89, 96, 108	98	5, 6, 82, 88, 89	14, 106	99-103	106, 17		
	↔					7						
	↓										107	110-114
Obesity	↑	9, 92, 94	12, 81, 84, 85		7, 8, 89, 90, 96	97	7, 8, 89, 90	15, 106	10, 104	106		
	↔											
	↓										107	111-112
Cardiovascular disease	↑	10	13, 81, 86, 87	94	8, 11, 95	11	8, 95	109	105			
	↔			95								
	↓							16, 109				115

Table 1. Altered Cytokines in Schizophrenia and Metabolic Disease. Studies showing increase (↑), decrease (↓) or no change (↔) in cytokines are indicated. The numbers refer to the abbreviated references cited below.

6. Conclusion

Much work has focussed on investigating altered neuronal morphology and synaptic function in

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