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Herpes viruses and neuroinflammation

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Chapter 11

Using nuclear medicine to unravel the etiology of schizophrenia: a focus on herpes viruses

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In preparation

Schizophrenia is a chronic and disabling brain disease that affect approximately 1% of the human population worldwide [1]. The symptoms of schizophrenia are classified into positive symptoms, such as delusions and hallucinations, negative symptoms, such as social withdrawal and flattened emotion, cognitive symptoms and mood symptoms. Despite extensive research, it is not known what causes schizophrenia or how the causative factors lead to the clinical symptoms. Environmental factors are thought to play a role in the etiology of schizophrenia, causing schizophrenia only in individuals with a genetic predisposition. Related to the environmental factors, viruses have been proposed to be involved in the etiology of schizophrenia.

Herpes viruses, large DNA viruses of which eight types are known to cause disease in humans, are most frequently associated with schizophrenia. These viruses have the ability to establish latency in the human body after primary infection. Reactivation of these viruses can occur due to a variety of factors at any point in life. However, the concept of herpes virus latency is complex and not fully understood. The sites in the human body where herpes viruses were found to establish latency include lymphocytes, monocytes and neuronal ganglions, depending on the type of herpes virus, but it has been proposed that these viruses also establish latency within the brain. Reactivation of these viruses within the brain causes neuronal damage, which could lead to the clinical symptoms resembling those of schizophrenia. The herpes simplex virus type-1 (HSV-1) is the most common cause of viral encephalitis that mainly involves the temporal lobe and limbic structures. HSV-1 encephalitis patients present with changes in consciousness, confusion and can also reveal psychosis similar to that in the prodromal phase of schizophrenia [2]. Imaging studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have shown hyperperfusion of the affected brain areas in early HSV-1 encephalitis, which was followed by progressive hypoperfusion [3,4]. In addition, a neuroinflammatory process beyond the primary focal lesion has been found in HSV-1 encephalitis patients, using PET [5]. Although HSV-1 encephalitis usually is an acute necrotizing encephalitis, mild forms of encephalitis have also been reported [6]. Schizophrenia was hypothesized by us to represent a mild form of herpes encephalitis.

The challenge in unraveling the role of herpes viruses in schizophrenia is to provide direct evidence for this hypothesis. Up to date, the only attempt to provide direct evidence for the presence of herpes viruses in the schizophrenic brains was by studying post-mortem brains [7]. The majority of these studies could not detect herpes viruses in the brain and in those who could, no differences were found between

healthy controls and schizophrenic patients. The negative results of these studies can be attributed to the attempt to detect herpes viruses many years after onset of schizophrenia. In addition, post-mortem studies in general do not discriminate between latent and actively replicating herpes viruses.

In order to further elucidate the role of herpes viruses in schizophrenia, non-invasive imaging techniques, such as PET and SPECT, can be of value for providing both indirect and direct evidence. Indirect evidence for the role of herpes viruses in schizophrenia could be obtained by imaging of processes in the brain that are influenced by the presence of herpes viruses. Imaging of neuroinflammation could be used to measure viral activity indirectly. Neuroinflammation is characterized by the presence of activated microglia cells, which show an increased expression of the peripheral benzodiazepine receptor (PBR). The PET tracer [^{11}C]-PK11195 is a PBR ligand and has been used to study neuroinflammation in many neurological diseases and could also be used for monitoring of disease progression and therapy response [8]. Recently, [^{11}C]-PK11195 PET showed the presence of global neuroinflammation in recent-onset schizophrenic patients, when compared to healthy volunteers [9]. In this study, patients were not experiencing psychosis at the time of the PET scan. However, with the viral hypothesis in mind it seems plausible that a viral infection of the brain causes focal neuroinflammation, especially during psychosis. Therefore, a [^{11}C]-PK11195 PET study was performed in schizophrenic patients that were scanned during psychosis [10]. Consistent with our hypothesis, focal neuroinflammation was found to be present in the hippocampus of schizophrenic patients, which is of particular interest in relation to the preference of HSV-1 to infect the temporal lobe and limbic structures. Although the presence of neuroinflammation does not provide evidence for a viral infection in the schizophrenic brain, it can be used as a tool to monitor treatment response in future studies. If the detected neuroinflammation is indeed caused by the presence of active herpes viruses, anti-viral treatment could be effective in reducing neuroinflammation.

In order to study the role of herpes viruses in schizophrenia directly, the availability of a PET tracer that images a specific characteristic of replicating herpes viruses or herpes virus infection is essential. The PET tracer 9-(4-[^{18}F]-fluoro-3-hydroxymethylbutyl)guanine ([^{18}F]-FHBG) and others were originally developed as imaging agents for monitoring of gene therapy with the HSV thymidine kinase reporter gene. [^{18}F]-FHBG is the radiolabelled analogue of the antiviral pro-drug penciclovir. The antiviral properties of penciclovir are based on the expression of viral

thymidine kinase (or a viral analogue) by active, replicating viruses. [^{18}F]-FHBG, like penciclovir, is phosphorylated by the viral thymidine kinase and remains trapped in the infected cell, allowing for localized imaging and quantification of viral activity. It is important to know that the endogenous human thymidine kinase has high substrate specificity and does not phosphorylate [^{18}F]-FHBG. Since penciclovir treatment was found to be effective against six out of the eight types of herpes viruses, these herpes viruses can likely be imaged with [^{18}F]-FHBG. It was recently shown in a rat model of herpes encephalitis that [^{18}F]-FHBG was suitable for the *ex vivo* detection of HSV-1 infection of the brain [11].

The finding that [^{18}F]-FHBG could detect active herpes viruses in the rat brain led to the start of a human study in schizophrenic patients [12]. In a first approach, schizophrenic patients were studied that were a priori divided into mildly and severely affected group, based on severity of psychosis and memory disorder. An important aspect of this study was that these patients were scanned during active psychosis. Based on the similarity between HSV-1 induced psychosis in herpes encephalitis and psychosis related to schizophrenia, it was hypothesized that if herpes viruses are present in the schizophrenic brain they would be more active during severe psychosis. Indeed, a significantly higher phosphorylation rate of [^{18}F]-FHBG was found in the temporal lobe of severely affected schizophrenic patients (as based on the PANSS and memory impairment), when compared to mildly affected patient. Interestingly, neuroinflammation was particularly found in the hippocampus, which is a part of the temporal lobe. The increased phosphorylation rate of [^{18}F]-FHBG could not be attributed to a single herpes virus, but the result of the [^{18}F]-FHBG study suggests the presence of active herpes viruses and supports the viral hypothesis of schizophrenia. Although [^{18}F]-FHBG suggests the presence of active herpes viruses in the temporal lobe of schizophrenic patients, its brain uptake is on general low and it is therefore a far from ideal tracer for brain imaging.

Despite the evidence that supports the viral hypothesis of schizophrenia that was provided by PET, further research is necessary to elucidate the exact role of herpes viruses in schizophrenia. Only then treatment strategies can be improved. Because PET and SPECT are non-invasive imaging techniques used for studying functional processes in the body, they can play an important role in providing further evidence for the viral hypothesis of schizophrenia. In addition, PET can be used for studying other psychiatric or neurological disorders in which neuroinflammation and/or viruses are hypothesised to play a role, such as depression, bipolar disorder and

Alzheimer's disease. With [^{18}F]-FHBG and [^{11}C]-PK11195 PET a first step was taken in providing evidence for the viral hypothesis of schizophrenia. However, the PET tracers that were used to study a viral infection in the human CNS have substantial limitations and future studies therefore require the development of new PET tracers with better image characteristics. These can include new PET tracers for imaging of neuroinflammation that are more sensitive than [^{11}C]-PK11195, which are already receiving a lot of attention, or for imaging of other aspects of the neuroinflammatory response to viral infection, like cyclooxygenase-2 and cytokine expression. Important for providing direct evidence of infection are PET tracers for viral thymidine kinase with better access to the CNS or that target different processes of viral replication. Many PET and SPECT studies on schizophrenia are nowadays focussed on the imaging of neurotransmitter systems that are implicated in schizophrenia. Among these, imaging of dopaminergic neurotransmission has received the most attention, since dopamine is proposed to play an important role in schizophrenia. PET and SPECT tracers have been developed for imaging of dopamine synthesis (e.g. [^{18}F]-DOPA), the dopamine transporter (e.g. [^{123}I]-FP-CIT), dopamine D₂ (e.g. [^{11}C]-raclopride, [^{123}I]-IBZM) and D₁ (e.g. [^{11}C]-SCH-23390) receptors [13,14]. While glutamatergic neurotransmission is also thought to be disturbed in schizophrenia, there is no suitable PET or SPECT tracer for imaging glutamatergic neurotransmission, yet. Imaging of dopaminergic and glutamatergic, as well as serotonergic, GABA-ergic and other, neurotransmitters system can also be of importance in unravelling the role of herpes viruses in schizophrenia. Especially when neurotransmitter disturbances can be linked to the presence of viruses or neuroinflammatory processes in the brain.

Thus, future research is necessary to provide additional and conclusive evidence for the viral hypothesis of schizophrenia. PET can be of great importance in these future studies, especially if more potent PET tracers for imaging viruses and viral processes in the CNS can be developed.

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