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Review

Avian influenza and the brain—Comments on the occasion of resurrection of the Spanish flu virus

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Abstract

Recent incidences of direct passage of highly pathogenic avian influenza A virus strains of the H5N1 and H7N7 subtypes from birds to man have become a major public concern. Although presence of virus in the human brain has not yet been reported in deceased patients, these avian influenza subtypes have the propensity to invade the brain along cranial nerves to target brainstem and diencephalic nuclei following intranasal instillation in mice and ferrets. The associations between influenza and psychiatric disturbances in past epidemics are here commented upon, and the potentials of influenza to cause nervous system dysfunction in experimental infections with a mouse-neuroadapted WSN/33 strain of the virus are reviewed. This virus strain is closely related to the Spanish flu virus, which is characterized as a uniquely high-virulence strain of the H1N1 subtype. The Spanish flu virus has recently been reconstructed in the laboratory and it passed once, most likely, directly from birds to humans to cause the severe 1918–1919 pandemic.

Keywords: Infections; Nervous system; Substantia nigra; Parkinsonism; Behavior; Schizophrenia

Contents

1. Introduction

A terror of the past, the virus of the Spanish flu of 1918–1919, has now been reconstructed in the laboratory [45]. Most likely,

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an influenza A virus strain passed directly from a bird to a human being, after which it adapted to the new host to cause the pandemic [41]. Avian influenza is very common, but crossing the species barrier to humans is an extremely rare event. In fact, until recently the barrier between birds and humans was thought to be too great to allow a direct transmission of the virus [52], although all mammalian influenza viruses may originate from ancestral precursors in wild water-fowls [13]. In light of the current incidents in South-East Asia and the Netherlands, in which humans have been infected with avian influenza virus strains [47], the nature of the species barrier and the risks for its by-pass have come into focus. Furthermore, since certain avian influenza virus strains can invade the brain of experimental animals [31], the question whether influenza poses a threat to our brains can be raised [46].

During pandemics in the past, including the Spanish flu, debates were spurred whether influenza is associated with psychosis or neuropsychiatric disorders, and there is a current controversy among epidemiologists whether influenza during pregnancy is a risk factor for schizophrenia in the offspring, or not. In this commentary the early literature on these possible associations will be briefly reviewed, as will factors that may facilitate a spread of the virus from its primary site of infection, the respiratory tract, to the brain and its potential to cause changes in brain gene expression, synaptic activities and behavior.

2. Human influenza pandemics and nervous system dysfunctions

2.1. Post-influenza psychosis in past pandemics

Except for observations of "febrile or initial delirium", mental disturbances in connection with influenza were not described before the 19th century according to Althaus [1]. Then in 1846, case-books report from the Dundee asylum on a "*decided increase in the suicidal melancholic cases*", the servants being more severely attacked than the patients, after influenza first visited Scotland [32]. This early observation was referred to in the intense debate on patients with psychiatric disturbances that included depression, manic conditions, amentias, acute delirious states, hysterical reactions, ideas of persecution and hallucinations during the 1889–1990 influenza pandemic [32]. Skepticisms on these reports were expressed and "*the ready acceptance of influenza as the cause of so many supposed cases of insanity*" was protested [42]. Melancholia seems, however, to have been especially prevalent and an asylum report from this period says that "*the epidemic of influenza* 1889–1990 *left the European world's nerves and spirits in a far worse state then it found them*" [9].

Few pandemics in modern times have within such a short period, 1918–1919, killed so many individuals as the Spanish flu. The mortality rate was about 2–3% and the estimated number of deaths varies between 20 and 40 millions or more. This was several times more than the death toll of soldiers during the First World War; the appearance of influenza in the troops weakened so much the fighting abilities of the armies that it contributed substantially to the end of the war [27]. During the Spanish flu pandemic, post-influenza psychosis was reported both in Europe and in USA. In a study of about two hundred cases of psychoses at the Boston Psychopathic Hospital, one-third showed symptoms similar to schizophrenia, but the majority of these patients recovered completely [23]. The few patients who showed no evidence of recovery may have represented latent schizophrenia precipitated by the influenza, and Bleuler in1924 (cited in [23]) stated that "*neither the grippe nor the war have added to the existence of schizophrenia*".

A major problem with these early attempts to associate influenza with psychiatric disorders is the lack of reliable statistics and standardized clinical diagnostic criteria. In addition, influenza A virus was not identified until it was isolated in ferrets in 1933 by Wilson and Smith [27]. During later years, anecdotal reports of acute psychotic symptoms, i.e. anxiety, confusion, extreme restlessness, ideas of perpetuation and senses of strange, unpleasant smells, have appeared following the Asian influenza in 1957. The symptoms usually receded within 6–8 days, leaving the patients with amnesia of the psychotic episodes (review, see [34,51]). Although reversible post-influenza psychosis may be recognized, its pathogenesis as well as its potential relation to other psychiatric disorders is not clear. However, these debates from past epidemics may stimulate interest in research on effects of influenza virus infections on the brain as expressed in a voice of 1892 stating "*we could not have a more interesting subject*" [48].

2.2. von Economo encephalitis: post-encephalitic Parkinsonism and behavior disturbances—was there any relation to influenza?

In 1916–1927, the world was hit by another pandemic and the disease of this pandemic affected the brain, i.e. *encephalitis lethargica* or von Economo encephalitis. The most prominent inflammatory lesions occurred in the midbrain tegmentum and substantia nigra. Inflammation localized anteriorly in the lateral wall of the third ventricle was observed in patients with insomnia, while in the posterior wall in patients with sopor [50]; a topography that predicted recent hypothesis on diencephalic regulation of sleep [33]. Post-encephalitic Parkinsonism was common and in these patients nerve cell loss and neurofibrillary tangles were seen in the substantia nigra and substantia innominata, the raphe, locus coeruleus, mesencephalic periaqueductal grey matter and hypothalamus [44].

Long-lasting behavior disturbances could appear, particularly in children, either directly after a hyperkinetic phase of the encephalitis or after a time period of recovery. These changes were characterized by manic phases with increased locomotion, and sleep disturbances with attacks of anxiety at night and sleepiness during daytime. Previously normal children became very talkative, obtrusive, disrespectful and unrestrained; they disgraced other people, became asocial, and had outbreaks of anger. They were witty, accosted people on the streets, pinched their clothes, shouted words of abuse and scrawled on walls [49].

Although certain epidemiological studies have pointed out a relation to Spanish flu [29], no proof of such a relationship has been obtained [30]. The Spanish flu did not break out in the world until 1918, i.e. 2 years later than *encephalitis lethargica* appeared, and recent attempts to isolate influenza RNA from archive brains of patients affected by *encephalitis lethargica* or postencephalitic Parkinsonism have been negative [18,21].

These observations indicate that an infectious disease can cause long-lasting psychiatric disturbances. The cause of *encephalitis lethargica* remains a mystery, although sporadic cases still appear and evidence for basal ganglia autoimmunity has been presented [10]. How antibodies against basal ganglia can cause neurofibrillary changes in distinct diencephalic and upper brainstem nuclei remains to be clarified.

2.3. Influenza encephalitis and encephalopathy

Clinical signs of encephalitis may in rare cases complicate influenza infections. For instance, 26 out of 359 verified cases of viral encephalitis in Finland in 1995–1996 were ascribed to influenza [15]. Only rarely have viruses between recovered from the brain or cerebrospinal fluid (CSF), which may be normal or show only a moderate inflammatory response, in patients with post-influenza encephalitis [34,51]. An acute encephalopathy in children, characterized by bilateral thalamic necrosis in CT scans, has appeared in Japan during the last decade and each year more than 100 cases have been reported. The disorder is distinct from Reye's syndrome, which occurs after a longer incubation period, and is associated with the administration of aspirin and characterized by low levels of glucose and high levels of ammonium in the blood. Influenza viral RNA is not detected in the CSF by PCR in most of the Japanese cases (reviews, see [25,38]). High levels of cytokines such as interleukin-6 and tumor necrosis factor-α have been found in sera and CSF, and such cytokines have been proposed to play a pathogenetic role [25,43]. It is not clear whether the severe encephalopathy is a "tip of an iceberg" and if children with milder brain affections exist. Neither is it clear why the thalamic nuclei should be particularly vulnerable to the insult [5], nor why such cases have been observed mainly in Japan. About one-third of the children die from the encephalopathy, and reports on possible psychiatric disturbances in the survivors, when they reach adulthood, still have to wait.

On this basis, the questions can be posed whether influenza has the propensity to invade the brain or whether encephalitis in humans mainly reflects an immune reaction (a perivenous encephalomyelitis)? Which are the mechanisms behind the non-inflammatory necrotic encephalopathies and to what extent do metabolic disturbances or release of inflammatory molecules from the site of infection in the respiratory tracts play a role in the brain dysfunctions? A systemic release of inflammatory cytokines may, for instance, be the cause of the severe muscle pain during influenza. The following section will focus on experimental studies showing that certain subtypes or strains of influenza virus can invade the brain to infect subpopulations of neurons and cause functional disturbances in rodents.

3. Molecular determinants for spread of influenza between species and within an individual

3.1. How can avian influenza spread from birds to humans?

In aquatic birds, which are the major reservoir of influenza, the virus infects the intestinal tract and is transmitted via the faeces. The infection is usually asymptomatic and very common: up to 20% Canadian wild juvenile ducks were found to be virus carriers when they congregated before migration [51]. Some influenza A viruses can be highly virulent in birds and cause fowl plaques, and some viral strains with a low pathogenicity in one species of birds may occasionally cause outbreak of disease in another species [13]. Influenza may cause an asymptomatic infection in ducks, loss of egg production in hens, and lethal infections in chicken and turkeys. One of the viral envelope proteins, the hemagglutinin (HA), plays a particularly important role for the spread of influenza.

Influenza A viruses are classified according to the antigenicity of two of their envelope proteins, HA and neuraminidase (NA) (Fig. 1). There are 16 different types of HA (H1–H16) and 9 types of NA (N1–N9). All subtypes are maintained in aquatic birds, but so far only the H1, H2 and H3 subtypes of the virus have been transmitted among humans to cause epidemics (review, see [13]). In the recent outbreaks, the avian influenza strains H5N1, H7N7 and H9N2 have been directly transmitted from birds to humans, but not with certainty between humans. The viral HA binds to a target cell surface receptor, which contains sialic acid. Human influenza binds to a α(2,6) sialic acid cellular receptor in human tracheobronchial epithelium, while avian influenza binds to receptors terminating in α(2,3)-linked sialic acid in bird epithelia.

The species barrier imposed by the HA–receptor interactions may be circumvented in two ways. The virus can either pass through an intermediate host, the pig, which expresses both α(2,3)- and α(2,6) sialic acid receptors in the respiratory epithelium and is therefore susceptible to both avian and human influenza. Since influenza virus has a segmented genome, reassortment of viral genes can readily occur if a cell is infected with two different viruses. Thus, an avian influenza virus may acquire HA genes from a human pathogenic strain, whereby the pig serves as a "mixing vessels" to generate avian-human reassortants, e.g. the viruses causing the Asian (1957) and Hong Kong (1968) influenza. Alternatively, the receptor specificity is only "preferential" and exposure to high viral titers may possibly overcome the barriers, or a few cells may express α(2,3) sialic acid receptors even in the human tracheobronchial tract to sustain an initial infection [13]. The virus then has to express an HA that recognizes α(2,6) sialic acid for efficient transmission among humans, as a necessary step. Such an evolution of the virus may occur and the lesson from the Spanish flu shows that an avian virus can adapt to humans to cause pandemics, although this is an extremely rare event.

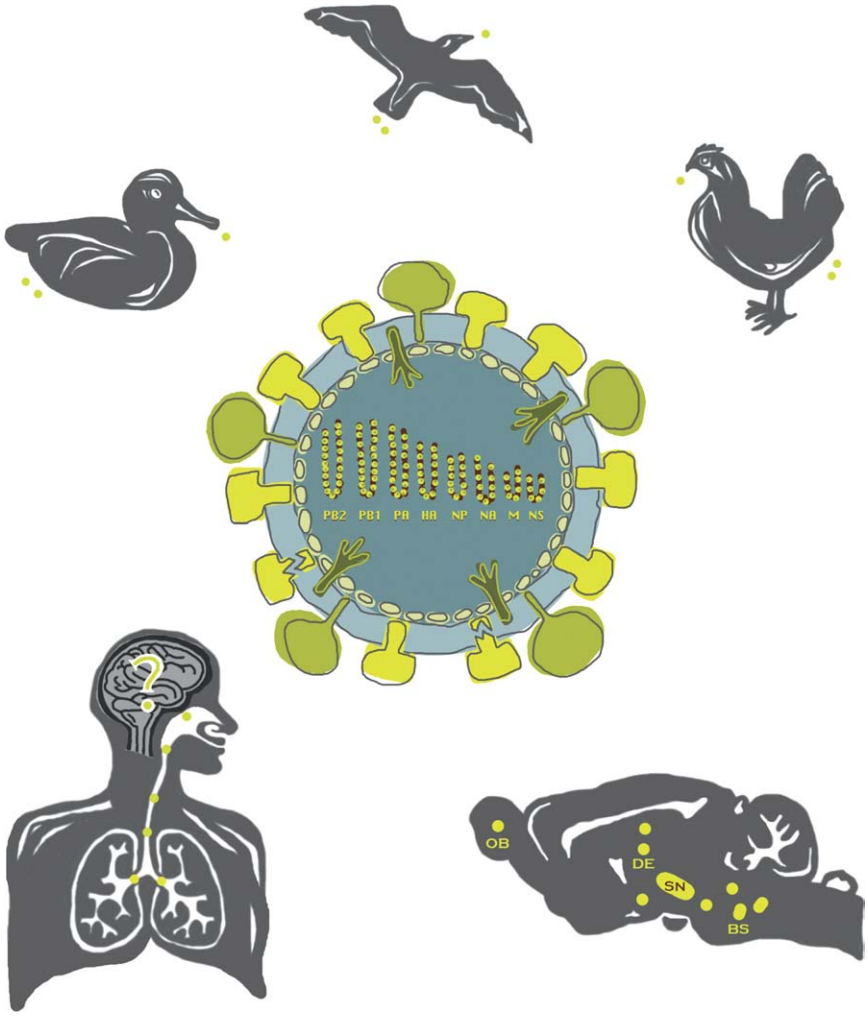

Fig. 1. Schematic drawing of avian influenza virus and its reservoir hosts, the birds, in which it causes intestinal infections with fecal secretion of the viruses (above). A direct transmission of the virus from birds to humans has recently occurred to cause severe tracheobronchial infections or conjunctivitis. It is not yet clear whether the virus can attack the human brain, but several isolates from infected individuals are highly neurotropic in mice after intranasal instillation (yellow-green marks infected areas in the olfactory bulb (OB), diencephalon (DE), substantia nigra (SN) and brain stem (BS)). The eight viral segmented genes encode three polymerase proteins (PB2, PB1 and PA), a nucleoprotein (NP), matrix proteins (M1 and M2), two envelope glycoproteins (HA (light green) and NA (dark green; the former has to be cleaved by host animal proteases to cause an infection)) and non-structural proteins (NS).

3.2. Can influenza spread from the respiratory epithelium to the brain?

Influenza virus buds from the apical surface of an epithelial cell by which the virus is released into the respiratory pathways for spread to other individuals, and only rarely does it spread into blood vessels to cause viremia. Influenza virus infections are also associated with induction of high levels of cytokines, including interferon-α/β, which prevents spread of the virus by inducing anti-viral states in neighboring, uninfected cells [11].

Particular interest has been linked to proteases in viral pathogenesis. The HA in the virus particles not only plays a role in binding the virus to a cellular receptor, but it also enables the viral envelope to fuse with host cell membranes to release viral genes into the cell for viral replication. HA is in a precursor form that has to be cleaved by a protease to become activated. Low pathogenic avian viruses possess a single arginine at the cleavage site in the HA molecule, rendering it susceptible to only a few "trypsin-like" proteases with an expression restricted to the respiratory or intestinal tracts, or both. Highly pathogenic avian strains, on the other hand, possess a series of basic amino acids at this site rendering it susceptible to proteases that are ubiquitous in the organism. A carbohydrate chain in the NA may also affect HA cleavage; for instance, a mouse-neuroadapted strain, WSN/33, that originates from the first H1N1 influenza A virus isolate [34] lacks such a chain due to a point mutation. This enables plasminogen, the precursor of plasmin, to come in close contact with NA to be activated and cleave HA. Since plasminogen is ubiquitous, the virus can replicate in several extrapulmonary tissues, including the brain.

The Spanish flu virus was an H1N1 subtype and the recently reconstructed virus could, like the WSN/33 strain, replicate in the absence of trypsin. However, it did not have either a series of basic amino acids at the HA cleavage site or mutations in the NA similar to the WSN/33 strain. Most likely, it was an entirely avian-like virus that adapted to humans, and not a reassortant

virus as seen in later pandemics. Following intranasal instillation in mice, the reconstructed virus grew to very high titers in the lung, but not to detectable levels in brain, heart, liver and spleen. The other proteins of the avian influenza virus are also important for its pathogenicity as, for instance, shown in experiments with reassortants of genes encoding the internal polymerases PB1 and PB2 [13]. An avian-like PB1 gene, as seen in the Spanish flu and the last two influenza pandemics, may provide a replicative advantage to the virus [41]. The exceptional virulence in the lung of the Spanish flu virus has been attributed to a constellation of properties in all eight genes [45]. It should be noted that certain bacterial proteases may activate HA, and a co-infection with bacteria is therefore an additional pathogenic threat.

Spread of influenza to the brain is therefore facilitated when the virus expresses an HA that can be cleaved by ubiquitous proteases. The H5 and the H7 avian influenza subtypes can both evolve into highly virulent viruses by acquiring additional amino acids at the HA cleavage site. Highly pathogenic avian influenza of these subtypes can spread along cranial nerves to the brain after intranasal instillation of the virus in mice. A spread along these pathways was first shown by Reinacher et al. [31], who co-infected cell cultures with a human and an avian influenza A virus, which yielded a recombinant virus. Following intranasal instillation in mice, this reassortant infected neurons in the olfactory bulbs and trigeminal ganglia as well as in nuclei in the brainstem. A hematogenous spread was ruled out, since neutralizing serum antibodies could not inhibit the spread. Subsequently, a H5N3 virus originating from a whistling swan and passaged in chicks was highly neurotropic after intranasal instillation in mice. Viral antigens were found in the vagal and trigeminal ganglia before they became widely distributed in the brainstem and diencephalic nuclei that included the nucleus of the solitary tract, the reticular nucleus of the medulla oblongata, nucleus ambiguus, dorsal raphe, substantia nigra and hypothalamic nuclei [36].

The outbreak in Hong Kong 1997 was caused by a highly pathogenic influenza A virus of the H5N1 subtype that passed directly from birds to humans. Two out of four isolates of this virus could replicate extrapulmonary and were neurotropic without prior adaptation in mice [19]. These two isolates spread along olfactory routes and/or trigeminal vagal and sympathetic nerves to the mouse brain following intranasal instillation [28,40]. Virus was not recovered from other extrapulmonary organs in mice, while in ferrets the viruses spread not only to the brain but to several other extrapulmonary organs as well [53].

The H5N1 viruses continued to circulate in geese in Southeastern China, where they reassorted with viruses of aquatic avian origin, and multiple genotypes of highly pathogenic reassortants appeared in the Hong Kong poultry market in 2001 [17]. Four out of five such reassortants could be isolated from the brain after a single intranasal passage in mice, which shows that highly neurotropic variants can be rapidly selected in mice [17]. Interestingly, even a majority of low pathogenic H5N1 isolates from human and avian species were detected in olfactory bulbs following intranasal instillation in mice and ferrets [20]. Little is known about the pathogenesis of H5N1 in humans. Although there has been no direct evidence of a systemic infection, no detailed report on potential involvement of the brain has yet appeared [40].

Avian influenza may also cause encephalitis in felids, as demonstrated in a tiger and a leopard in a Thailand zoo, which showed histological signs of encephalitis after eating H5N1-infected poultry carcasses [14]. Highly pathogenic avian H7 viruses have been isolated from seals, horses and a human victim of an H7N7 outbreak in the Netherlands. A mouse lung-adapted H7N7 isolate from a horse spread along cranial nerves to the mouse brain, and targeted diencephalic and brainstem nuclei similarly to those by the H5N1 subtypes [37].

4. Functional disturbances and gene expression changes in the brain in experimental influenza virus infections

4.1. Changes after olfactory route spread of the mouse-neuroadapted WSN/33 influenza A virus strain

The spread of avian influenza along the olfactory route is of particular interest, since this route links the limbic system to neurons in the olfactory epithelium, which are directly exposed to the external environment. In experimental animals olfactory neurons can be infected following intranasal instillation of influenza virus, and possibly also in humans, since a common cause of disturbances in olfaction is a previous influenza-like infection [12].

In the author's laboratory, effects on gene expression in the brain and on animal behavior by influenza targeted to the brain along this route using the mouse-neuroadapted WSN/33 strain have been analyzed. Following intracerebral inoculation in mice, the virus causes a lethal infection with abundant viral antigens in the substantia nigra and ventral tegmental area (VTA) [39]. Following inoculation into the olfactory bulbs, a non-lethal infection ensues and the virus is targeted to the medial habenular nuclei, midline thalamic nuclei, VTA and dorsal raphe nuclei. The viral infection is cleared in wild-type mice and no trace of viral RNA can be detected 35 days post-infection (p.i.) [24]. Such mice show disturbances in anxiety-related behavior and an elevated transcriptional activity of two genes encoding synaptic regulatory proteins, regulator of G-protein signaling 4 and calcium/calmodulindependent protein kinase IIa, in diencephalic structures when examined 14–20 weeks after the infection [6]. These studies show that influenza virus can cause long-term behavior disturbances and altered gene expression in the brain by a "hit and run" mechanism.

4.2. Can a maternal influenza virus cause alteration in the offspring brain?

4.2.1. Maternal influenza virus infections and schizophrenia

Since the report in 1988 of an increased incidence of schizophrenia in individuals born of mothers who were in the second trimester of pregnancy during the time of the 1957 influenza pandemic [22], a large number of epidemiological studies have aimed at linking maternal influenza virus infections to psychiatric diseases in the offspring. Even nowadays

this connection has not firmly been established, since several studies have failed to replicate the association between maternal influenza and schizophrenia (review, see [26]). However, epidemiological studies still indicate influenza during pregnancy as a risk factor for schizophrenia in adult life and maybe mood disorders [16] as do, yet to be confirmed, serological studies [8].

4.2.2. Experimental infections

To answer the question whether influenza can cause changes in brain functions following a maternal infection, experiments employing two different mouse-neuroadapted influenza viruses have been used, NWSN/33 and WSN/33 (NWSN/33 is another mouse-neuroadapted strain of the first H1N1 isolate of 1933 [34]). The NWS/33 did not spread from the lungs to the fetuses following intranasal instillation in pregnant mice, which showed severe signs of disease, had a high mortality rate of the fetuses and gave birth to pups with reduced birth weight. These offspring showed severe behavioral changes that included disturbances in pre-pulse inhibition [35]. Since similar behavior disturbances in the offspring could be produced by intraperitoneal injection of poly I:C, which is a potent inducer of cytokines, the effects on the fetuses were attributed to maternal inflammatory antiviral responses rather than to the virus itself [35].

Using the highly neuroinvasive WSN/33 strain, viral proteins as well as viral RNA were found in the brains of the fetuses 3 days after intranasal virus instillation in pregnant mice at day 14 of gestation [3]. Depending on the viral dose administered, the newborn pups either died during the first week of life, or survived with no overt signs of disease or disturbances in locomotor activities. However, when examined at 90 and 280 days of age, but not before, altered expression of two genes in the offspring brains could be verified by PCR after screening with a small micro-array of 1176 genes [4]. This shows that a maternal infection can cause gene expression changes in the brain that appear only when the offspring reaches early adulthood.

4.3. Can influenza virus persist in the brain after an infection and can viral proteins disturb synaptic functions?

Human influenza A viruses are associated with acute, and in general not with persistent, infections both in man and in immunocompetent experimental animals. For several infectious agents, the mammalian brain presents a favorable environment for persistence: it is an immune-privileged site with a blood–brain barrier that may protect from circulating antibodies and neurons that normally do not express major histocompatibility complex (MHC) class I molecules rendering them insensitive to cytotoxic T cells. To persist, RNA viruses need a low grade replication of its components in the tissues, since, in contrast to DNA viruses, they can not be incorporated into the host cell genome.

Such a balance between influenza virus replication and host defenses may be maintained in brains of immunodeficient mice with deletion of the gene of transporter associated with antigen presentation (TAP), which is a molecule that presents viral peptides to MHC class I for T cell recognition. The WSN/33 influenza A virus strain inoculated into olfactory bulbs of such mice spread to nuclei in the brain similarly to infected wild-type mice, as described above [24]. However, the virus is not eliminated and viral proteins can be detected immunohistochemically in the VTA 1 month later [24]. Viral mRNA encoding the viral NP and NS-1 proteins, in particular, are detected by PCR at the midbrain levels 10–17 months days p.i. [2]. Thus, this strain of influenza virus can persist in the brain of immunodeficient individuals. In a fraction of offspring to pregnant mice intranasally infected with this virus strain, viral RNA can also be detected in the brains at postnatal day 90 [3].

Since mRNA encoding the NP protein is most readily detected in the brains harboring a persistent influenza virus infection, in the author's laboratory it was examined whether NP expression in a neuron can have functional consequences. In cultured hippocampal neurons, the NP protein accumulates in dendritic spines. When introduced by coupling to a non-toxic HIV-TAT fragment as a tranducer, long-term exposure of cultures to NP causes reduced amplitude, but not reduced frequency, of the spontaneous synaptic activity [7]. These experimental studies show the influenza virus components may, under certain circumstances, persist in the brain for extended periods of time after an infection and that such components may cause functional disturbances at the synaptic level.

5. Concluding remarks

Due to species barriers, mainly residing in the virus HA—host cell receptor recognitions, passage of the virus from birds to humans is an extremely rare event, but lessons from the Spanish flu and recent outbreaks indicate that the barriers may be leaky and a direct spread from birds to humans of highly pathogenic virus strains is nevertheless possible.

Avian strains are often neurotropic and can spread to the brain along cranial nerves and target several nuclei in the diencephalon and brainstem, including the substantia nigra, in both mice and ferrets. Brain infections with influenza viruses may be non-lethal and by a "hit-and-run" mechanism they may cause behavior disturbances in experimental animals and gene expression changes in the mouse brain. Gene expression changes in the brain may also be a late event, which does not to appear until offspring to influenza-infected pregnant mice reach early adulthood. In immunocompromised hosts, the virus may persist in the brain and postsynaptic functions can be affected in neurons harboring viral components. Thus, in experimental models certain influenza virus strains have the propensity to invade the brain, cause changes in gene expression and synaptic functions, and behavior disturbances. It should, however, be emphasized that these observations on nervous system dysfunctions in mice caused by influenza infections only point out potentials by which a virus can affect the brain. So far, there is no report that avian influenza can spread to the brain in humans and any association between influenza and neuropsychiatric disorders remains to be established. However, since neurotropic variants of influenza can rapidly be selected in mice, this virus may be a threat imposed by nature also to the human brain. A fight against this terror should therefore be a concern also for neuroscientists.

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