



## Review

# Human coronaviruses: Viral and cellular factors involved in neuroinvasiveness and neuropathogenesis



Marc Desforges\*, Alain Le Coupanec, Jenny K. Stodola, Mathieu Meessen-Pinard, Pierre J. Talbot\*\*

Laboratory of Neuroimmunovirology, INRS-Institut Armand-Frappier, Institut national de la recherche scientifique, Université du Québec, 531 boulevard des Prairies, Laval, Québec, Canada H7V 1B7

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## ABSTRACT

Among the various respiratory viruses infecting human beings, coronaviruses are important pathogens, which usually infect the upper respiratory tract, where they are mainly associated with common colds. However, in more vulnerable populations, such as newborns, infants, the elderly and immunocompromised individuals, these opportunistic pathogens can also affect the lower respiratory tract, leading to pneumonia, exacerbations of asthma, and various types of respiratory distress syndrome. The respiratory involvement of human coronaviruses has been clearly established since the 1960s. Nevertheless, for almost three decades now, data reported in the scientific literature has also demonstrated that, like it was described for other human viruses, coronaviruses have neuroinvasive capacities since they can spread from the respiratory tract to the central nervous system (CNS). Once there, infection of CNS cells (neurotropism) could lead to human health problems, such as encephalitis and long-term neurological diseases. Neuroinvasive coronaviruses could damage the CNS as a result of misdirected host immune responses that could be associated with autoimmunity in susceptible individuals (virus-induced neuroimmunopathology) and/or viral replication, which directly induces damage to CNS cells (virus-induced neuropathology). Given all these properties, it has been suggested that these opportunistic human respiratory pathogens could be associated with the triggering or the exacerbation of neurologic diseases for which the etiology remains poorly understood. Herein, we present host and viral factors that participate in the regulation of the possible pathogenic processes associated with CNS infection by human coronaviruses and we try to decipher the intricate interplay between virus and host target cells in order to characterize their role in the virus life cycle as well as in the capacity of the cell to respond to viral invasion.

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\* Corresponding author. Tel.: +450 687 5010x4342; fax: +450 686 5501.

\*\* Corresponding author. Tel.: +450 687 5010x4300; fax: +450 686 5501.

E-mail addresses: [marc.desforges@iaf.inrs.ca](mailto:marc.desforges@iaf.inrs.ca) (M. Desforges), [pierre.talbot@iaf.inrs.ca](mailto:pierre.talbot@iaf.inrs.ca) (P.J. Talbot).

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## 1. Introduction

Viral infections of the respiratory tract represent a major problem for human and animal health around the world. These respiratory infections induce the most common illnesses (Vareille et al., 2011) and are a leading cause of morbidity and mortality in humans worldwide, especially children, the elderly and immune-compromised individuals (Cesario, 2012; Ison and Hayden, 2002; Jartti et al., 2012; Sloots et al., 2008). The idea that viruses can cause respiratory tract infections has been demonstrated since the early 1930s (Jartti et al., 2012). Nevertheless, with the help of modern diagnostic tools, a significant number of new respiratory viruses have been discovered since the beginning of the 21st century and it is estimated that there are about 200 antigenically distinct viruses able to cause infection of the respiratory tract, especially in infants and children (Brouard et al., 2007). In fact, it is now believed that viruses cause 95% of respiratory diseases in children and infants and about 30–40% in the elderly (Jartti et al., 2012). Among the various respiratory viruses, coronaviruses are important pathogens of humans and animals. Most of the coronaviruses that infect human beings usually reach the upper respiratory tract, where they are mainly associated with symptoms of common colds. However, being opportunistic pathogens, they can also affect the lower respiratory tract in more vulnerable populations, such as newborns, infants, the elderly and immune-compromised individuals, where they can lead to pneumonia, exacerbations of asthma, respiratory distress syndrome or even severe acute respiratory syndrome (SARS) or Middle-East respiratory syndrome (MERS) (Raj et al., 2014; Vabret et al., 2009).

Even though the airway epithelial cells of the respiratory tract represent a first line of defense against pathogens, they can become a target for infection by several different respiratory viruses, as a way for them to penetrate the human host. Several infections of epithelial cells, including those that involve coronaviruses, are self-limited and the infection remains local as the virus will be cleared by the immune system in the respiratory tract, with minimal clinical consequences. However, in some circumstances, opportunistic viral pathogens like the human coronaviruses can avoid the immune response and cause more severe respiratory diseases (Vareille et al., 2011) or even spread to other tissues, including the central nervous system (CNS), where they could induce other types of pathologies (McGavern and Kang, 2011). Human coronaviruses are molecularly related in structure and mode of replication with neuroinvasive animal coronaviruses (Brian and Baric, 2005) such as PHEV (porcine hemagglutinating encephalitis virus) (Greig et al., 1962), FCoV (feline coronavirus) (Foley et al., 2003), and MHV (mouse hepatitis virus) (Lampert et al., 1973), which have all been shown to invade the CNS and induce different types of neuropathologies. The MHV, represents the best described case of coronaviruses involved in neurological diseases and several excellent reviews have highlighted the importance of both viral and host factors in the process (Bender and Weiss, 2010; Cowley and Weiss, 2010; Hosking and Lane, 2010). MHV can also persist in the mouse CNS and induce a chronic demyelinating disease, which is partially immune-mediated, similar to what is observed in multiple sclerosis (MS) in humans (Hosking and Lane, 2010; Weiss and Leibowitz, 2011). Therefore, the close structural and biological relatedness of human coronaviruses to the neurotropic animal coronaviruses has led to speculation about possible involvement of human coronaviruses in neurological diseases. Because they are

themselves also naturally neuroinvasive in humans and mice, a possible association between the presence of ubiquitous human coronaviruses in the establishment or the exacerbation of neurological human pathologies has over the years been suggested.

Up until now, no clear specific association has ever been made with any known human neuropathology. However, even though the mechanism by which they reach the human CNS is still to be decrypted, at least three of the six coronaviruses that infect humans were shown to be neuroinvasive and neurotropic in humans: HCoV-229E and HCoV-OC43 (Arbour et al., 1999a, 1999b, 2000; Bonavia et al., 1997), as well as SARS-CoV (Gu et al., 2005; Xu et al., 2005).

Even though this association between coronavirus infection of the CNS and human diseases remains circumstantial and even to a certain degree controversial, the current review aims at presenting interesting and important data that clearly illustrates the natural neuroinvasive potential of these human pathogens and underlines that further research is warranted in order to better characterize the real impact of coronavirus infection of the human CNS on human health.

## 2. Coronaviruses: an overview

Coronaviruses display a characteristic crown-shaped appearance, are widespread in nature and can infect several different species (Vabret et al., 2009), in which they cause mainly respiratory and enteric pathologies, with neurotropic and neuroinvasive properties in various hosts including humans, cats, pigs, rodents and fowl (Buchmeier and Lane, 1999; Cavanagh, 2005; Talbot et al., 2011). They form a group of enveloped viruses that have the largest genome among RNA viruses. This non-segmented 30 kb positive-single-stranded polyadenylated RNA possesses 4 or 5 genes encoding structural proteins (S, E, M, N; HE for several members of the Betacoronavirus genus) and several genes encoding non-structural proteins, mostly comprised in ORF1a and 1b, which encode two polyproteins (pp1a and pp1ab) that are cleaved by two viral proteases to yield 15 to 16 non-structural proteins (nsp), including the RNA-dependent RNA polymerase (RdRp), helicase and exonuclease, which all play a role in viral replication (Gorbalenya et al., 2006; Lai and Cavanagh, 1997).

### 2.1. Viral molecular determinants of pathogenesis

The spike protein (S) is a large type 1 transmembrane glycosylated protein responsible for recognition of the cellular receptor used by the virus to infect a susceptible cell (Cavanagh, 1995). During infection of susceptible hosts, the S protein represents an important factor of virulence as it appears to be associated with most of the cytotoxic effects that lead to degeneration of infected cells following infection by different coronaviruses (Brison et al., 2011, 2014; Favreau et al., 2009, 2012; Iacono et al., 2006; Jacomy et al., 2010; Phillips et al., 1999, 2002).

The envelope (E) protein is a small structural protein anchored in the viral envelope and which has a role in the morphogenesis, trafficking within the infected cells and budding of the virion, and which appears responsible for the curvature of the viral envelope (Liu et al., 2007; Ruch and Machamer, 2012). Similarly to the S protein, but in a different manner, it also represents a virulence factor: during infection of host cells, it appears to be associated with the induction of the cell stress response and apoptosis (DeDiego et al., 2011; Nieto-Torres et al., 2014), and it

may be associated with disruption of the lung epithelium after a SARS-CoV infection (Teoh et al., 2010) and participate to the SARS-CoV-associated immunopathology in the respiratory tract (Jimenez-Guardeno et al., 2014).

The membrane (M) protein interacts with all the other structural proteins of the virus and therefore helps to shape and maintain the structure of the virion (Hogue and Machamer, 2008; Neuman et al., 2011). During infection of cells, this protein can participate in the virus-induced inhibition of the type 1 interferon response by the infected cells (Siu et al., 2009; Yang et al., 2013) and therefore influence the outcome of infection and cell fate after infection.

The nucleocapsid (N) protein associates with the viral genome and plays an essential role in encapsidating it in a helical nucleocapsid within the viral particle (Hogue and Machamer, 2008; Macneughton and Davies, 1978). It also is an RNA chaperone that facilitates template switching during replication of the genome and transcription of the sgRNA (Zuniga et al., 2010, 2007). The N protein of SARS-CoV was shown to partially localize to the nucleolus (You et al., 2005), and to deregulate the host cell cycle (Li et al., 2005a). Moreover, like the M protein, the N protein of different coronaviruses can participate in the inhibition of type 1 interferon response by the infected cell and in the induction of apoptosis (Ding et al., 2014; Kopecky-Bromberg et al., 2007; Surjit and Lal, 2008; Ye et al., 2007).

The hemagglutinin-esterase (HE) is only present in species of the betacoronavirus genus. Like the S protein, it is a type 1 transmembrane protein which forms homodimers (Hogue and Machamer, 2008) and which may interact with different types of acetylated sialic acid (de Groot, 2006). It may be important early during infection or during the release of viral particles from the infected cells at the end of the replication cycle of the betacoronaviruses (Rottier, 1990). Moreover, its acetyl-esterase activity strongly enhances the production of infectious virions, which can disseminate in murine mixed primary CNS cultures (Desforges et al., 2013a). Coronaviruses also possess non-structural (ns) or accessory proteins that appear to mainly play a role in pathogenesis and in the virus-host interactions (Narayanan et al., 2008) as well as in virulence and tropism associated with the capacity to replicate in different cell types and organs (Cruz et al., 2011; Dedeurwaerder et al., 2013; Koetzner et al., 2010; Zhao et al., 2013, 2012, 2011).

## 2.2. Human coronaviruses: recognized respiratory pathogens

Human coronaviruses (HCoV) were first isolated in the mid-60s from patients with upper respiratory tract disease (Myint, 1995). In 1965, Tyrrell and Bynoe isolated the first HCoV (B814 strain) that was able to cause a common cold in human volunteers after intranasal inoculation (Tyrrell and Bynoe, 1965). Shortly thereafter, Hamre and Procknow (1966) isolated the prototype HCoV-229E strain, and McIntosh and collaborators (1967) were able to identify various viruses, which comprise the now recognized prototype HCoV-OC43 strain (Hamre and Procknow, 1966; McIntosh et al., 1967).

Up until the Severe Acute Respiratory Syndrome (SARS) appeared in China during the fall of 2002 and was associated with SARS-CoV (Drosten et al., 2003; Fouchier et al., 2003; Ksiazek et al., 2003), serological studies only distinguished between two groups of HCoV, namely HCoV-229E (previous group 1, now classified in the Alphacoronavirus genus) and HCoV-OC43 (previous group 2, now classified in the Betacoronavirus genus). Since the SARS outbreak of 2002, research on coronaviruses have entered a new era, which led to the identification of several new coronaviruses, including three that infect humans. Namely, they are HCoV-NL63 (van der Hoek et al., 2004) in the genus Alphacoronavirus, HCoV-HKU1, which is part of the Betacoronavirus genus (Woo et al., 2005) and

more recently, MERS-CoV, a newly identified Betacoronavirus (Zaki et al., 2012).

The HCoV-229E, -OC43, -NL63 and -HKU1 strains all present a worldwide distribution and genetic variability, as they exist in different genotypes (Dominguez et al., 2012; Gerna et al., 2006; Lau et al., 2011; Vabret et al., 2006; Vijgen et al., 2005; Woo et al., 2006). These four strains are endemic in humans and infections mainly occurs in winter and early spring (Cabeca et al., 2013; Gaunt et al., 2010; Larson et al., 1980; Myint, 1995), in different parts of the world (Chiu et al., 2005; Mackay et al., 2012; Theamboonlers et al., 2007; Vabret et al., 2009). Most of the times, they infect the upper respiratory tract, where they are mainly associated with rhinitis, laryngitis or otitis but, as opportunistic pathogens, in more vulnerable populations such as newborns, infants, the elderly and immune-compromised individuals, they can also reach the lower respiratory tract, where they could instead be associated with bronchitis, bronchiolitis, pneumonia, exacerbations of asthma, respiratory distress syndrome (Talbot et al., 2008; Vabret et al., 2009).

The 2002–2003 SARS pandemic was caused by a coronavirus variant that appears to have emerged from a bat reservoir (Li et al., 2005b) to infect palm civets, sold live in open markets, the intermediary reservoir, and then to humans (Guan et al., 2003). During this pandemic, a total of 8096 probable cases were reported and almost 10% (774 cases in more than 30 countries) of these resulted in death (Braden et al., 2013; Cherry, 2004). After an incubation period, the typical clinical portrait was described by a flu-like syndrome, followed by a respiratory syndrome first associated mainly with cough and dyspnea before the “real” severe acute respiratory syndrome (SARS) took over in about 20% of the patients (Vabret et al., 2009). Furthermore, a typical pathological portrait of the respiratory tract showed edema, hemorrhage and congestion of the lungs, as well as pleural effusion in the thoracic cavity associated with infiltration of immune cells (van den Brand et al., 2014). Multiple organ failure was also observed in several SARS-CoV-infected patients (Gu et al., 2005; Vabret et al., 2009).

Recently, in the fall of 2012, ten years after the SARS episode, a SARS-like disease affected individuals that traveled from the Arabian Peninsula to the United Kingdom. Using molecular sequencing, it was rapidly shown that this new respiratory coronavirus was genetically different than SARS-CoV and it is now recognized that the new epidemic is caused by a new coronavirus from the genus Betacoronavirus (Zaki et al., 2012), that was first named HCoV-EMC (for Human Coronavirus – Erasmus Medical Center), human betacoronavirus 2c and NCoV or nCoV (for novel Coronavirus), and that is now known under the official name MERS-CoV: Middle-East Respiratory Syndrome Coronavirus (Coleman and Frieman, 2013; de Groot et al., 2013), which is the etiologic agent of a severe lower respiratory tract infection that resembles SARS and which can be associated with gastrointestinal symptoms and possible renal failure (Raj et al., 2014). Like other coronaviruses that infect humans, MERS-CoV most likely originated from bats before infecting an intermediary reservoir (probably the dromedary camel in that case), and thus represents a zoonotic transmission to humans. However, human to human transmission has now been demonstrated in several cases (Assiri et al., 2013b; Haagmans et al., 2014; Raj et al., 2014). As of September 18th, 2014, the Public Health Agency of Canada revealed that the World Health Organization (WHO) has reported that the MERS-CoV has spread to at least twenty-one different countries, where 841 laboratory-confirmed cases of individuals (including 402 between April 11 and June 9, 2014 in Saudi Arabia alone) have been identified as infected by the MERS-CoV, with 298 being fatal (Public Health Agency of Canada, 2014). As do the four circulating strains of HCoV (Cabeca et al., 2013; Vabret et al., 2009), both SARS-CoV and MERS-CoV usually induce more (Assiri et al., 2013a; Hui et al., 2014) severe

illnesses in vulnerable populations such as the elderly, infants, immune-compromised individuals or patients with comorbidities (Peiris et al., 2004; Vabret et al., 2009).

Over the years, the four circulating HCoV have been associated with pathologies outside the respiratory tract, such as myocarditis and meningitis (Riski and Hovi, 1980) and severe diarrhea (Gerna et al., 1985; Resta et al., 1985), as seen with animal coronaviruses. Recent investigations on the HCoV as enteric pathogens demonstrated that all the HCoV can be found in stool samples of children with acute gastroenteritis but could not conclude on their “true association” with disease etiology (Esper et al., 2010; Risku et al., 2010). As previously mentioned, different reports have also presented a possible link between the presence of HCoV within the human central nervous system (CNS) and some neurological disorders (Arbour et al., 2000; Cristallo et al., 1997; Fazzini et al., 1992; Stewart et al., 1992; Yeh et al., 2004).

### 3. Neuroinvasive and neurotropic viruses

Several viruses have the ability to invade the CNS, where they can infect the resident cells, including the neurons. In fact, as stated by Big and colleagues (Big et al., 2009), even though the incidence of viral infections of the CNS is not well defined, they are not uncommon occurrences in clinical practice and an increasing number of positive viral identifications are now made with the help of modern molecular diagnostics. Using different routes of entry, several different viruses have been shown to be able to penetrate the CNS (neuroinvasion), where they can infect neurons and glial cells (neurotropism) and possibly induce or participate in the induction of neurological diseases (neurovirulence) (Giraudon and Bernard, 2010). In humans, a long list of viruses, for which the primary site of infection in human is not the CNS, possess these “neuroproperties” and neuroviral infection often leads to acute encephalitis, which can be fatal depending on virus tropism (Whitley and Gnann, 2002). For example, rabies virus (Hankins and Rosekrans, 2004), herpes simplex virus (HSV) (Aurelian, 2005), arthropod-borne flaviviruses such as West Nile virus (WNV) or Japanese encephalitis virus (JEV) (Mackenzie et al., 2004; Neal, 2014; Sips et al., 2012) and enteroviruses such as poliovirus (PV) and coxsackievirus (CV) (Mueller et al., 2005; Rhoades et al., 2011), affect millions of individuals worldwide each year and can induce encephalitis, meningitis and paralysis in humans. Chronic human neurological diseases and/or sequelae may also be linked to viral infection. In acquired immunodeficiency syndrome (AIDS) dementia and related disorders, human immunodeficiency virus (HIV) induces neurodegeneration (Mattson et al., 2005), which can result in motor dysfunctions and possibly cognitive impairments (Nath and Berger, 2004). Progressive multifocal leukoencephalopathy (PML) is a human demyelinating disease (Gordon et al., 2000) where prolonged immunosuppression leads to reactivation of latent polyoma JC virus (JCV) (Weissert, 2011). Human T-lymphotropic virus (HTLV-1) causes progressive tropical spastic paraparesis/HTLV-1-associated myelopathy (PTSP/HAM) in 1–2% of infected individuals (Kaplan et al., 1990) and HSV-1 and human herpes virus 6 (HHV-6) were proposed to cause or exacerbate Alzheimer’s disease (AD) (Itzhaki et al., 2004).

Respiratory viral agents also have the capacity to invade the human CNS where they will infect resident cells and potentially be neurovirulent in inducing a neuropathology. Several of these recognized respiratory pathogens can gain access to the CNS, where they can eventually cause health problems in humans.

#### 3.1. Respiratory viruses with neuroinvasive and neurotropic properties: associated neuropathologies

Respiratory syncytial virus (RSV), the most common pathogen to cause lower respiratory tract infection in infants worldwide

(Stensballe et al., 2003), is one such neuroinvasive respiratory agent that has been detected in the cerebrospinal fluid (CSF) of patients (Kawashima et al., 2009; Zlateva and Van Ranst, 2004) and that was associated with convulsions (Morichi et al., 2011), febrile seizures, and encephalitis (Millichap and Wainwright, 2009). Furthermore, it was recently shown that RSV can spread from the airways to the CNS in mice after intranasal inoculation, and that it induces behavioral and cognitive impairments (Espinoza et al., 2013).

Measles virus (MV), is another common virus that causes a disease of the respiratory airways associated with fever, cough and congestion. However, MV infection also induces other symptoms including a characteristic rash and Koplik’s spots (O’Donnell and Rall, 2010) in the oral mucosa. A second type of rare but significant sequelae is long-term CNS disease (O’Donnell and Rall, 2010). Post-infectious encephalomyelitis (PIE) or acute disseminated encephalomyelitis (ADEM) occurs in 1 of 1000 measles cases in children and adolescents. Measles inclusion body encephalitis (MIBE) is a second CNS complication that can arise after a MV infection in immune-compromised patients. Finally, subacute sclerosing panencephalitis (SSPE) is a third form of CNS disease associated with MV infection. It is a slow progressive neurological disease that appears 6–10 years after infection in about 4 to 11 cases per 100,000 cases of measles (for review see (Wilson et al., 2013)).

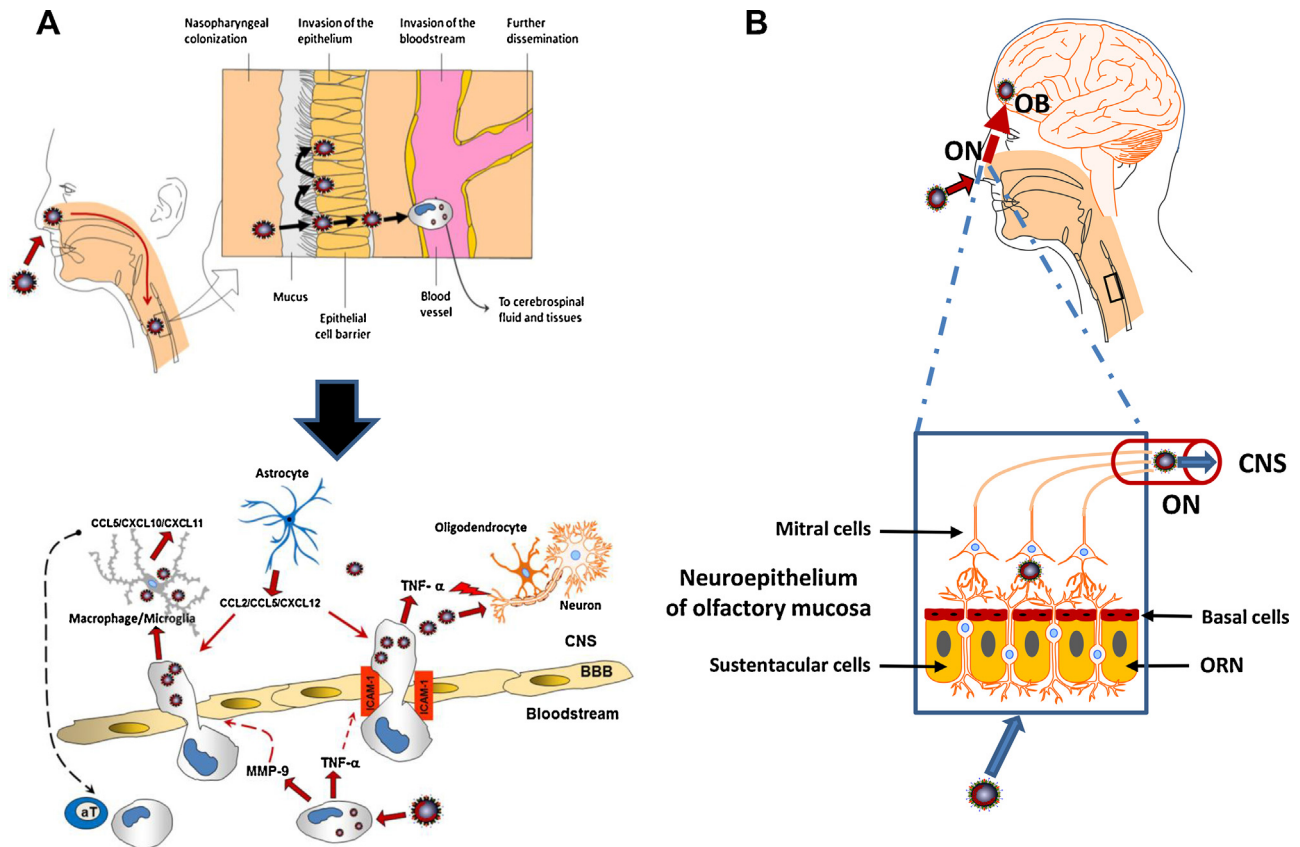
Hendra virus (HeV) and Nipah virus (NiV) represent important emerging viruses discovered in the 1990s (Escaffre et al., 2013) and cause acute and severe respiratory disease in humans, including necrotizing alveolitis with hemorrhage, pulmonary edema and pneumonia (Escaffre et al., 2013). Neurological signs of pathology include confusion, motor deficits, seizures, febrile encephalitic syndrome, and reduced level of consciousness. Moreover, neuropsychiatric sequelae have been reported but it is not known whether post-infectious encephalo-myelitis occurs following infection (Wong, 2010). The use of animal models showed that the main route of entry into the CNS is the olfactory nerve (Munster et al., 2012).

Influenza virus comes in three types: A, B, and C. Types A and B are most prevalent and cause the flu syndrome, characterized by chills, fever, headache, sore throat and muscle pains (Zeng et al., 2013), and are responsible for seasonal epidemics that affect 3–5 million humans, of which 250,000–500,000 cases are lethal each year (Kuiken et al., 2012). Most infections of influenza virus A are localized to the upper respiratory tract but some more severe cases may result in pneumonia (Nicholson et al., 2003) and even complications involving the CNS (Jang et al., 2009). Several studies have shown that influenza A can be associated with encephalitis, Reye’s syndrome, febrile seizure, acute necrotizing encephalopathy, and possibly acute disseminated encephalomyelitis (ADEM) in humans (Millichap and Millichap, 2006; Ozkale et al., 2012; Toovey, 2008; Wang et al., 2010; Zeng et al., 2013). Making use of murine models, it has also been shown that influenza A virus could reach the CNS through the olfactory nerve route and alter hippocampal morphology or expression of synaptic regulatory genes while impairing cognition and emotional behavior (Beraki et al., 2005; Jurgens et al., 2012). Influenza A virus was also described as a factor which may increase the risk of Parkinson’s disease (PD) (Jang et al., 2009).

As previously mentioned, among these different respiratory viruses that can reach the CNS where they could be associated with neurological symptoms in humans and animals, are the coronaviruses.

#### 3.2. Human coronaviruses in the CNS

Coronaviruses that infect humans are not well characterized concerning their capacity to invade and infect the CNS. However, the detection of coronaviral RNA in human brain samples clearly demonstrates that these respiratory pathogens are naturally



**Fig. 1.** Potential route of infection used by HCoV for neuroinvasion into the human central nervous system (CNS) and possible mechanisms of neurovirulence. (A) Following infection of human airways, human coronaviruses may, in some conditions, pass through the epithelium, gain access to the bloodstream and infect monocytes, which are activated by the infection. Among other factors, MMP9, which increases BBB permeability and TNF-alpha, which leads to up-regulation of ICAM-1 expression on endothelial cells, facilitates the passage of infected and activated monocytes into the CNS. Once in the CNS, these cells produce proinflammatory cytokines (such as TNF-alpha) that can damage the oligodendrocytes and/or the neurons. Infiltrated infected monocyte-derived macrophages (or microglia) may produce chemokines (CCL-5, CXCL10, CXCL11), which will induce chemoattraction of activated T cells and/or other monocytes. After sensing the infection, astrocytes may also produce other chemokines (CCL2, CCL5 and CXCL12) that will also participate in the recruitment of more infected leukocytes. Human coronaviruses may therefore initiate an aberrant neuroinflammatory loop which will mediate an immune-mediated neuropathology (adapted from Talbot et al., 2008). (B) Following intranasal infection in human, coronaviruses may infect the olfactory receptor neurons (ORN) and pass through the neuroepithelium of the olfactory mucosa to reach the mitral cells and the olfactory nerve (ON) and gain access to the olfactory bulb (OB) and eventually to the hippocampus and other regions of the brain.

neuroinvasive in humans and suggests that they establish a persistent infection in human CNS (Arbour et al., 2000). Furthermore, we have shown that these viruses are able to establish a persistent infection in human cells representative of the CNS (Arbour et al., 1999a, 1999b) and that HCoV-OC43 RNA could be detected for at least a year in the CNS of infected mice that survived the acute encephalitis. A significant portion of these surviving mice exhibited abnormal reflexes shown by limb claspings, presented clinical signs of decreased activity in an open field test, and had a smaller hippocampus associated with a loss of hippocampal neurons, particularly in the CA1 and CA3 layers (Jacomy et al., 2006), similar to what is seen after neuroinvasion of the CNS by the influenza A virus (Jurgens et al., 2012). Therefore, an apparently innocuous human respiratory pathogen may persist in the human CNS and it would therefore be possible that such a persistent infection may become a factor or co-factor of neuropathogenesis associated with long-term neurological sequelae in genetically or otherwise predisposed individuals.

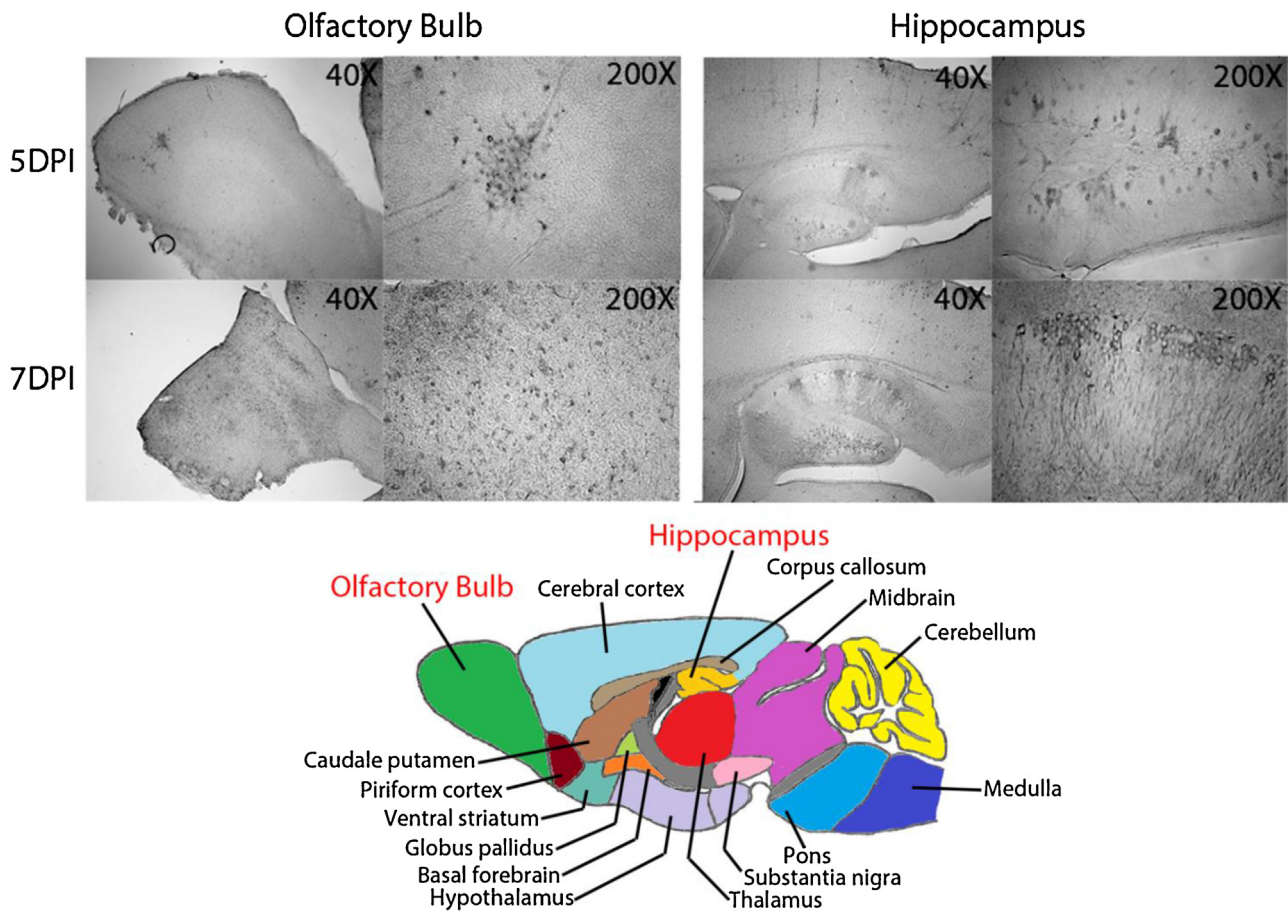
### 3.2.1. Possible mechanisms of coronavirus neuroinvasiveness

Viruses may enter the CNS through two distinct routes: hematogenous dissemination or neuronal retrograde dissemination. Hematogenous spread involves the presence of a given virus in the bloodstream and retrograde viral spread toward the CNS

happens when a given virus infects neurons in the periphery and uses the transport machinery within those cells in order to gain access to the CNS (Berth et al., 2009).

In order to be neuroinvasive, human coronaviruses may use both CNS entry routes from the periphery. The hematogenous route involves the presence of a given virus in the blood where it can either remain free for a period of time before it infects endothelial cells of the blood–brain barrier (BBB), or infect leukocytes that will become a viral reservoir for dissemination toward the CNS. Both situations do occur during human immunodeficiency virus (HIV) infection of the CNS, as infected leukocytes migrate through the blood–brain barrier (BBB) (Kim et al., 2003), with direct infection of endothelial cells of the BBB having also been reported (Argyris et al., 2007). Human cytomegalovirus (HCMV) (Bentz et al., 2006; Chan et al., 2012), enteroviruses including poliovirus (Rhoades et al., 2011) and flaviviruses (Neal, 2014) have also been shown to infect different types of leukocytes and to use them as a reservoir for hematogenous dissemination toward the CNS.

In the human airways, it is still unclear what type of damage may be induced by HCoV in epithelial cells of the respiratory tract after infection. One report indicated that experimental intranasal inoculation of HCoV-229E to human volunteers led to disruption of the nasal epithelium, leading to damage of the ciliated cells and to a significant decrease in the number of cells and to a lowered



**Fig. 2.** Human coronavirus transneuronal route of neuroinvasion through the olfactory nerve and spread into the CNS in susceptible mice. Following intranasal infection or 14 day-old susceptible mice, HCoV-OC43 infects first the olfactory bulb (left panel) and then disseminate to other regions of the brain, including the hippocampus (right panel). In both regions of the brain, neurons are the main target of infection.

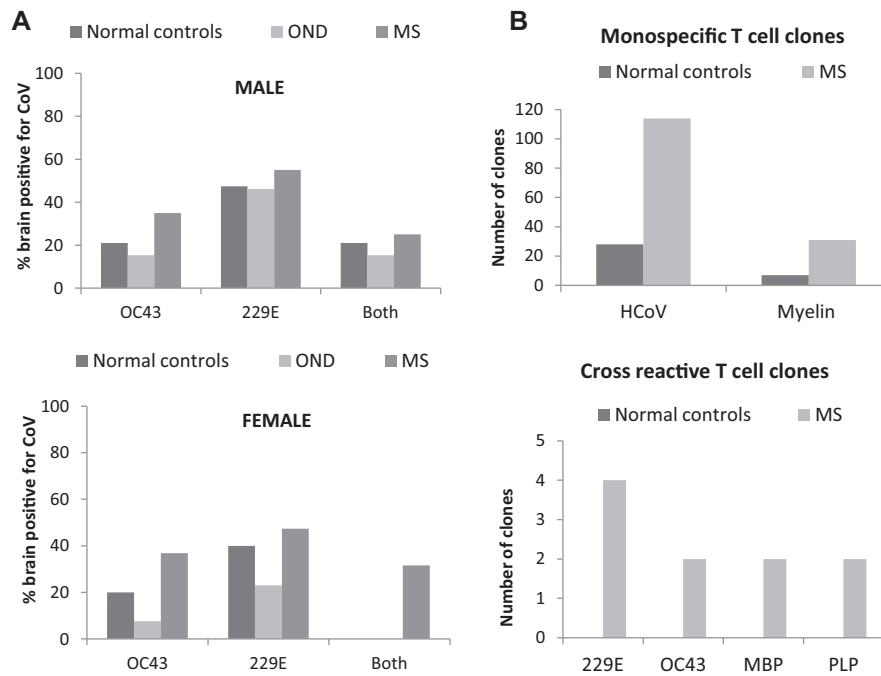
frequency of cilium beating (Chilvers et al., 2001). On the other hand, using primary cultures of cells from the human respiratory tract, Dijkman and collaborators were able to further characterize the interaction between HCoV and epithelial cells and detected no cytopathic effect. Even though they showed that after infection all four circulating HCoV strains were budding and released preferentially on the apical side of the cells, a low but significant amount of virus was also found to be released from the basolateral side (Dijkman et al., 2013). This suggests that, even though HCoV infection are, most of the time, self-restricted to the airway lumen since they do not induce important disruption of the epithelium, they may, under certain circumstances, pass through the epithelium barrier and gain access to the bloodstream or lymph, where they can infect leukocytes and consequently disseminate toward other tissues, including the CNS (Fig. 1A; adapted from Desforges et al., 2007; Talbot et al., 2008) as it has been suggested for other important human respiratory viruses; namely measles virus (Wilson et al., 2013), Nipah virus (Mathieu et al., 2011) and influenza B virus (Xu et al., 1998).

Infection of human monocytes/macrophages by HCoV-229E and HCoV-OC43 was reported (Collins, 2002; Desforges et al., 2007) and infection by HCoV-229E of human (Mesel-Lemoine et al., 2012) and murine dendritic cells expressing the human aminopeptidase N (Wentworth et al., 2005) suggests that HCoV may on one hand manipulate the immune system and on the other hand use dendritic cells to disseminate to other tissues, including the CNS, where they could be associated with other type of pathologies.

Human primary monocytes are activated following HCoV-229E infection (Desforges et al., 2007). Since they eventually

become macrophages as they invade tissues, this activation suggests that HCoV-229E-infected monocytes would serve to facilitate their passage toward other tissues including the CNS, especially in immune-compromised individuals, as this was observed for murine cytomegalovirus (MCMV) (Reuter et al., 2004). The fact that HCoV-229E could only infect partially immune-compromised transgenic mice (Lassnig et al., 2005) suggests that, being an opportunistic pathogen, HCoV-229E could take advantage of an immune-suppressed environment and disseminate to the CNS within susceptible individuals. The establishment of a persistent infection in a human leukocytic cell line (Desforges et al., 2007) is also consistent with the possibility that monocytes/macrophages serve as a reservoir and vector for this neuroinvasive HCoV (Arbour et al., 2000). The SARS-CoV was also shown to infect monocytes-macrophages (Gu et al., 2005; Nicholls et al., 2006) and dendritic cells, where it modulates innate immunity (Spiegel et al., 2006). These cells could also serve as a reservoir for virus to reach and maintain itself in the CNS. Our results indicate that HCoV are able to infect human endothelial cells of the BBB in culture (unpublished data). It has also been speculated that SARS-CoV could do the same after viremia (Guo et al., 2008). Therefore, neuroinvasive coronaviruses that infect humans could use the hematogenous route to penetrate into the CNS.

The second form of any viral spread toward the CNS is through neuronal dissemination, where a given virus infects neurons in periphery and uses the machinery of active transport within those cells in order to gain access to the CNS (Berth et al., 2009). After an intranasal infection, both HCoV-OC43 (Jacomy and Talbot, 2003) and SARS-CoV (McCray et al., 2007) were shown to infect the



**Fig. 3.** Detection of coronaviral RNA in human CNS and of HCoV-myelin antigens cross-reactive T cells in MS patients. (A) Double-blind analysis of ninety human brain autopsy samples revealed the presence of HCoV-229E and HCoV-OC43 RNA in normal controls, patients with other neurological disorders (OND) and patients with multiple sclerosis (MS). The proportion of brain samples from MS patients containing HCoV-OC43 RNA was significantly greater than OND and normal controls. RNA from both HCoV was found more often in Female brains compared to male. (B) More monospecific T-cell clones were isolated from MS patients compared to normal controls and cross-reactive T-cell clones were isolated only from MS patients.

Adapted from Arbour et al, 2000 and Boucher et al., 2007.

respiratory tract in mice and to be neuroinvasive as HCoV-OC43 (Butler et al., 2006; St-Jean et al., 2004) and SARS-CoV (Netland et al., 2008) were detected in the CNS of susceptible mice. Interestingly, the neurotropic MHV strains of the murine coronavirus (MuCoV) also reach the CNS through the olfactory nerve (Barnett and Perlman, 1993). Furthermore, as shown here in Fig. 2, once in the brain, HCoV-OC43 is able to disseminate from the olfactory bulb to other regions of the brain, including the cortex and the hippocampus, from which it appears to spread by a trans-neuronal route before it eventually reaches the brainstem and spinal cord (Desforges et al., 2013b). These results suggest that coronaviruses may also invade the human CNS from the external environment through the neuroepithelium of the olfactory nerve and olfactory bulb before infecting the resident cells of the brain, and potentially the spinal cord (Fig. 1B), as reviewed by Mori and colleagues for some neuroinvasive human viruses such as influenza virus, Herpes simplex virus (HSV), and borna disease virus (BDV) (Mori et al., 2005).

Like several human viruses listed previously in the present review, coronaviruses that infect human beings are naturally neuroinvasive and neurotropic and potentially neurovirulent as a result of misdirected host immune responses (virus-induced neuroimmunopathology) and/or viral replication, which directly induces damage to CNS cells (virus-induced neuropathology).

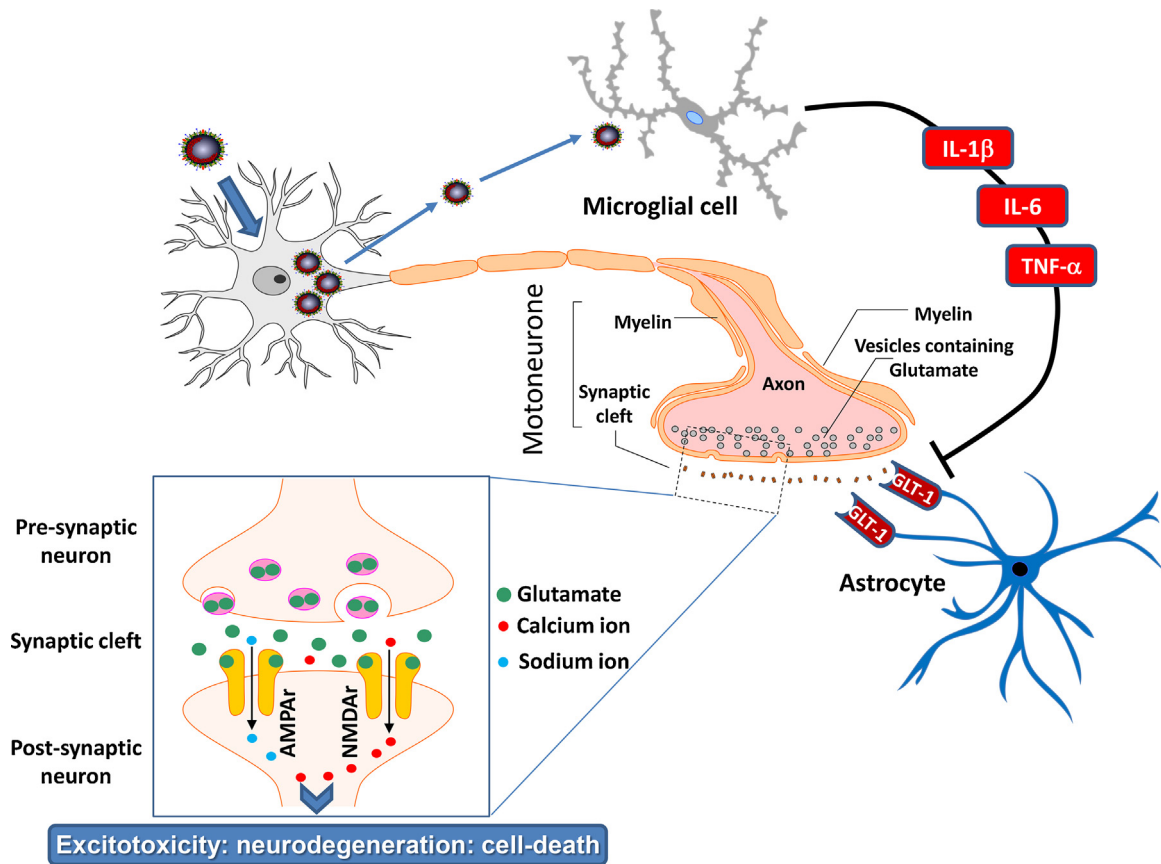
### 3.2.2. Mechanisms of HCoV-induced neurodegeneration: possible associated neuropathologies

Even though no direct association has ever been made with the onset of human neurological diseases, the presence of HCoV-229E and HCoV-OC43 was detected in various neurological diseases in humans, including Parkinson's disease (PD) and multiple sclerosis (MS) (Arbour et al., 2000), as well as ADEM (Yeh et al., 2004).

Multiple sclerosis truly represents a human neurological disease where an infectious agent or agents may play a triggering

role, with viruses the most likely culprit in genetically predisposed individuals (Kurtzke, 1993). There is a presumption that several neurotropic viruses could be involved in MS pathogenesis but that they may do so through similar direct and/or indirect mechanisms (Cusick et al., 2013; Gilden, 2005; Kakalacheva et al., 2011; Talbot et al., 2001). However, research has not yet led to a direct link to any specific virus or other microbes with MS. Association of coronaviruses with MS was suggested in numerous reports that are reviewed elsewhere (Desforges et al., 2013b). One of these reports demonstrated a significant association of colds with MS exacerbations and a significant association of HCoV-229E infection in MS patients (Hovaneec and Flanagan, 1983) and another report on the association of viral infections and MS (Sibley et al., 1985) commented that seasonal HCoV infection patterns do fit the observed occurrence of MS exacerbations.

We were previously able to confirm that HCoV-OC43 and HCoV-229E are naturally neuroinvasive in humans. Indeed, viruses were detected in some control brains and in some brains coming from patients different neurological diseases, including Alzheimer's and Parkinson's disease, there was a significantly higher prevalence of HCoV-OC43 in brains of MS patients (Arbour et al., 2000) and viral RNA was found more often in female brain samples (Fig. 3A). Even though this observation is only circumstantial, it is interesting to note that MS is more prevalent in women than in men (Bove and Chitnis, 2013). Moreover, this data, in association with the observation that autoreactive T cells were able to recognize both viral and myelin antigens in MS patients but not in controls during infection by HCoV-OC43 and HCoV-229E (Boucher et al., 2007; Talbot et al., 1996), suggest that the immune response may participate in the induction or exacerbation of neuropathologies such as MS in genetically or otherwise susceptible individuals (Fig. 3B). Furthermore, even though the use of the immunosuppressive drug cyclosporin A in HCoV-OC43-infected mice resulted in a faster onset of encephalitis, suggesting a role for T cells in viral clearance and



**Fig. 4.** HCoV infection induces increased production of proinflammatory cytokines and neuronal degeneration as a consequence of glutamate excitotoxicity. In physiological conditions, glutamate is mainly synthesized by neurons and released in the synaptic cleft as the primary excitatory neurotransmitter of the CNS that activates the ligand-dependant receptor AMPAR (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionoc acid receptor), which allows the entry of sodium ions and the passage of the nerve impulse in the post-synaptic neuron, leading to activation of the NMDA receptor (N-methyl-D-aspartate receptor) that allows the entry of calcium ions. During infection of neurons by HCoV-OC43, microglial cells detect the presence of virus and produce pro-inflammatory cytokines (TNF-alpha, IL-1 beta and IL-6) that down-regulate the astrocytic receptor GLT-1 (glutamate transporter 1) and prevent the efficient recapture of glutamate. This situation disturbs the regulation of glutamate homeostasis and the excess of this neurotransmitter in the synaptic cleft leads to excitotoxicity associated with a massive entry of calcium which eventually leads to degeneration of and death of neuronal cells.

survival with no related immunopathology (Jacomy et al., 2006), it was shown that in recombination activation gene (RAG) knock-out mice, HCoV-OC43-induced encephalitis could be partially mediated by the T-cell response to infection (Butler et al., 2006). The participation of different types of T cells has been shown to play a significant role in the demyelinating neurological disease induced by the murine CoV, in particular for strain MHV-JHM (Matthews et al., 2002). Furthermore, used as an experimental model of chronic viral infection associated with demyelination in the mouse CNS, this murine coronavirus has recently been shown to reflect partial oxidative tissue injury found in MS lesion in humans (Schuh et al., 2014), underlining the possibility that long term infection of the CNS by coronaviruses may induce MS-like lesions. This may also apply for persistence of HCoV RNA in the human CNS (Arbour et al., 2000), which in some conditions, could be associated with onset or exacerbation of neuropathologies, including MS.

Making use of another mouse model, we showed that HCoV-OC43 induced immune cell infiltration and cytokine production within the mouse CNS. This immune response was significantly increased after infection by virus variants which harbor mutations in the surface viral glycoprotein (S), consequent of viral persistent infection of human neural cells (Jacomy et al., 2010), and which induce glutamate excitotoxicity (Brisson et al., 2011, 2014). The increased cytokine production following infection by the S-mutant viruses may induce direct damage to neurons (Amor et al., 2010) and/or disturb glutamate homeostasis by down-regulating the

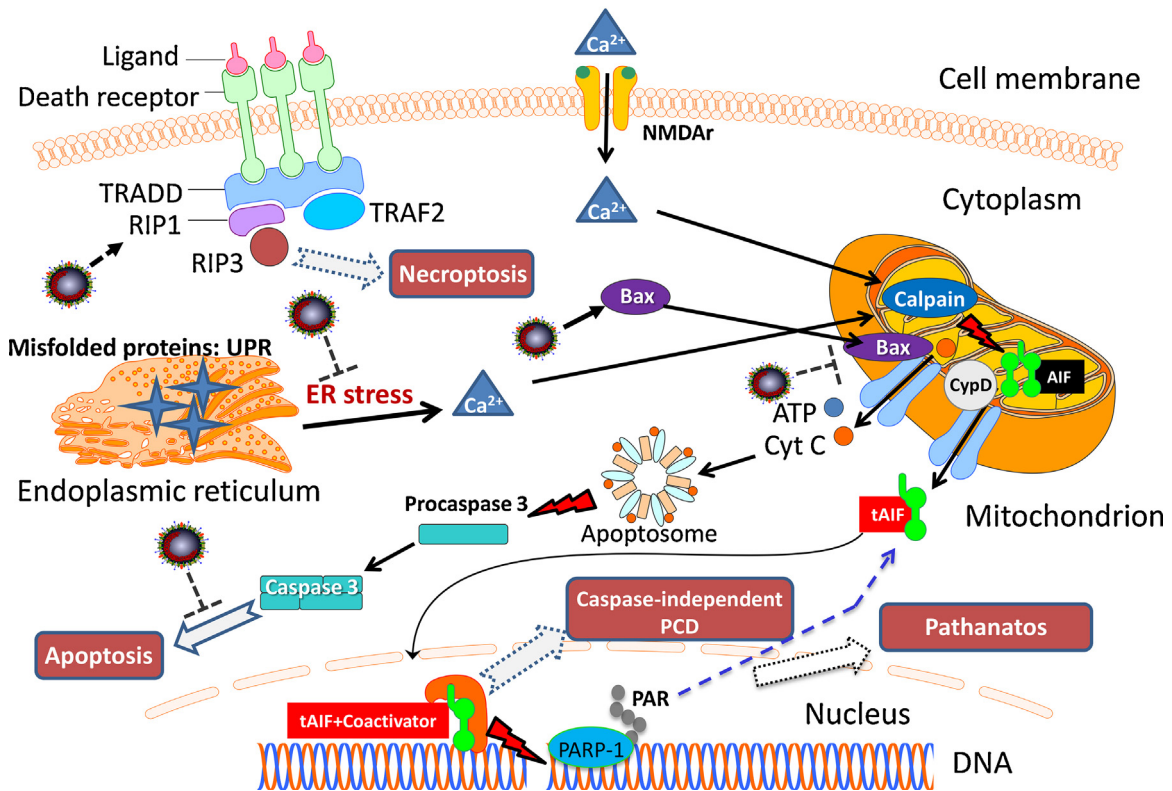
glutamate transporter GLT-1 on astrocytes that should recapture the excess of glutamate, which may generate glutamate excitotoxicity (Carmen et al., 2009) and thereby contribute to neuronal degeneration (Fig. 4; Brisson et al., 2011), which can be associated with hind-limb paralysis and possible demyelination (Brisson et al., 2011; Jacomy et al., 2010). The outcome of the observed degeneration of neurons may eventually be death of these essential cells.

As previously mentioned, infection of neurons by itself may also participate in the process of cell death by directly generating a cytotoxic insult related to viral replication and/or to the induction of different cell death pathways.

When present in the murine CNS, HCoV-OC43 infects neurons in different regions of the brain (Fig. 2), before reaching the spinal cord. Infection of these essential cells induces their degeneration as observed by aberrant state of neurofilament phosphorylation (Brisson et al., 2011, 2014; Jacomy et al., 2010), a situation that often leads to cell death and that could be directly induced by viral replication. Furthermore, using two model cell lines representing differentiated human neurons, we were able to demonstrate that programmed cell death (PCD) was induced after HCoV-OC43 infection (Favreau et al., 2009, 2012) and that the inhibition of viral replication was also in direct correlation with increased cell survival, suggesting that infection and production of progeny infectious viruses directly participate in the process of degeneration and eventual death of neurons. Our results indicate that the underlying mechanisms appear to involve different cellular factors and



## Mechanisms of neuronal cell-death

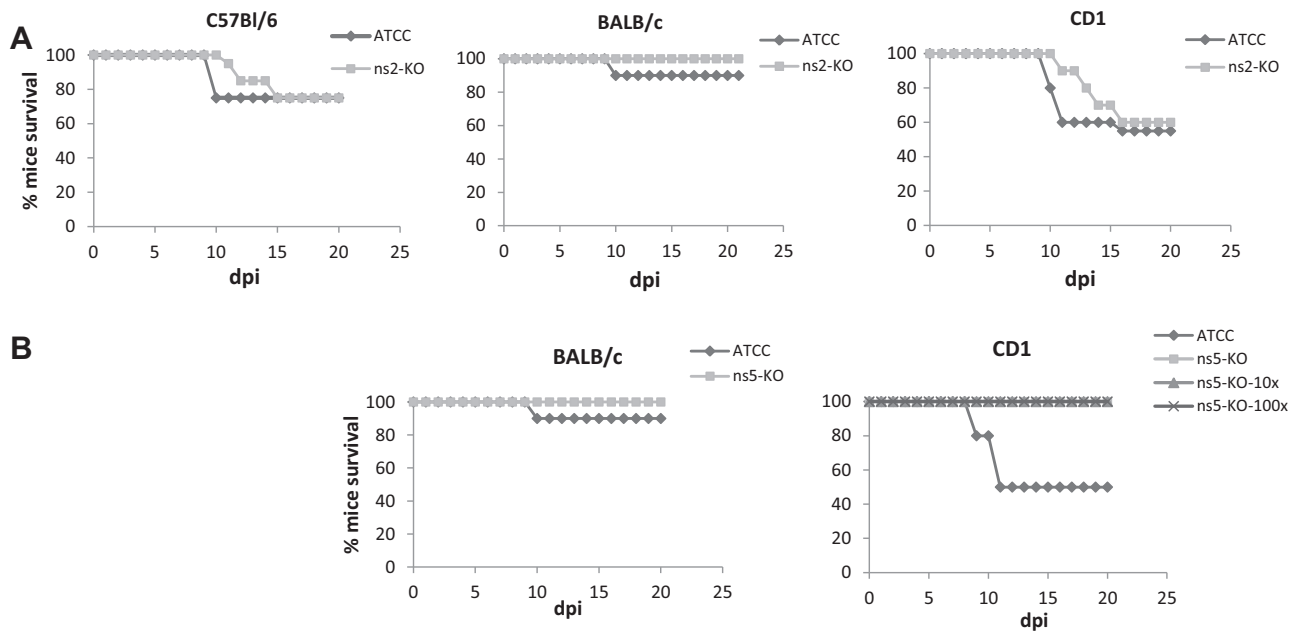


**Fig. 5.** Pathways of neuronal degeneration and programmed cell death (PCD) activated or potentially inhibited after HCoV-OC43 infection of neuronal cells. Hallmarks of apoptosis, including the relocalization of the activated pro-apoptotic protein BAX (Bcl-2 associated protein X) from the cytosol to the mitochondrial membrane, cytochrome C release from mitochondria toward the cytosol, DNA fragmentation and activation of caspases-3 and -9, are observed during infection of human neurons. However, even though virus induces Bax relocalization, it may inhibit classical apoptosis by blocking Bax pro-apoptotic function at the mitochondria and/or downstream of caspase activation, suggesting a caspase-independent type of apoptosis. Relocalization of the mitochondrial protein AIF (apoptosis-inducing factor) toward the nucleus (truncated tAIF) is observed after infection and participates in DNA fragmentation. AIF is known to be activated during caspase-independent apoptosis. However, AIF is also involved in Parthanatos, another form of PCD potentially associated with neurodegeneration. As they are synthesized by the poly(ADP-ribose) polymerase (PARP) during a neuronal stress, including during HCoV-OC43 infection, polymers of ADP-ribose (PAR) may relocalize toward mitochondria and participate in the activation and relocalization of AIF toward the cytosol before it reaches the nucleus. Cyclophilin D (CypD) inhibition decreases AIF release from mitochondria and abrogates cell death induced by infection. AIF release from mitochondria may be induced through its truncation (tAIF) by activated calpain, which is usually activated by a rise in the mitochondrial calcium concentration. This increase in calcium concentration may be linked with either an important entry from the extracellular milieu (for instance during glutamate excitotoxicity) or with a release of calcium from the ER following induction of ER stress. However HCoV-OC43 may inhibit the ER stress-related pathway in infected neurons. Infection induces RIP1 gene expression and the knock-down of the receptor interacting protein kinase-1 (RIP-1), significantly increases cell survival, suggesting that necroptosis, a third form of PCD which involves RIP-1 and RIP-3 downstream of the death receptor family, may play a role in HCoV-OC43-induced neuronal death. Solid arrows indicate experimental data and dashed arrows represent possible pathways based on the literature (see text for details).

pathways, including caspase-independent apoptosis, parthanatos and necroptosis, three forms of programmed cell death (PCD) reviewed elsewhere by the Nomenclature Committee on Cell Death (NCCD) (Galluzzi et al., 2012). These cell death pathways can act separately but may also interact in response to a stimulus (including a viral infection), as they share some of the cellular factors involved in the overall process that leads to cell death and that often converges toward mitochondria (Galluzzi et al., 2012). Fig. 5 is a tentative representation of the various pathways and cellular factors associated with PCD that may be activated and/or inhibited during HCoV-OC43 infection of neurons. It is based on our data (Brisson et al., 2011; Favreau et al., 2009, 2012; Jacomy et al., 2010) and on the scientific literature that describes some molecular pathways (parthanatos, necroptosis and apoptosis) and cellular factors, including calcium overload, endoplasmic reticulum stress, excitotoxicity, poly(ADP-ribose) polymerase (PARP) and calpain involved in mitochondrial dysfunction and eventual neurodegeneration and neuronal cell death (Cali et al., 2011; Galluzzi et al., 2012; Kaiser et al., 2013).

Virus-cell interactions are always important in the regulation of cell response to infection. For HCoV-OC43, we clearly showed

that the viral S glycoprotein is an important factor of neurovirulence and neurodegeneration of infected cells (Brisson et al., 2011; Favreau et al., 2009; Jacomy et al., 2010). This was similarly shown for the strains MHV-A59 and MHV-JHM of the MuCoV species, the murine counterpart of HCoV-OC43. Indeed, several reports and reviews have, over the years, shown that the S protein of this neuroinvasive and neurotropic murine coronavirus is a major factor associated with neurovirulence during encephalitis and the eventual demyelinating disease in susceptible mice (Bender and Weiss, 2010; Hosking and Lane, 2010). We have also demonstrated that the HE protein is an important factor for the production of infectious HCoV-OC43, suggesting an attenuation of the eventual spread into the CNS of viruses made deficient in fully active HE protein (Desforges et al., 2013a). Therefore, as the infection of neuronal cells and production of infectious virus apparently directly participate in the induction of neuronal death, the HE protein of HCoV-OC43 could play a role in neurovirulence of HCoV-OC43, like it does for MHV (Kazi et al., 2005). In recent years, several coronavirus accessory proteins, including the TGEV protein 7 and the MHV ns2 protein have been extensively studied and are now considered as important viral factors of virulence implicated in pathogenesis as



**Fig. 6.** Importance of HCoV-OC43 non-structural accessory proteins as neurovirulence factors in infected mice depends of the mouse strain. Groups of 20 mice (A) of three different strains were infected by the intracerebral route with reference wild-type HCoV-OC43 (ATCC) or with a mutant deleted for the ns2 accessory protein (ns2-KO) and (B) with reference wild-type HCoV-OC43 (ATCC) or with a mutant deleted for the ns5 accessory protein (ns5-KO). Infection with ten times (ns5-KO-10x) or even a hundred times (ns5-KO-100x) more ns5 mutant virus led to a reduced neurovirulence compared to wild type virus (ATCC). Survival was evaluated daily over a period of 21 days. Results are representative of two independent experiments.

they are able to counteract host-cell response associated with the activation of RNase L and the type 1 interferon response (Cruz et al., 2011; Zhao et al., 2013, 2012, 2011). Our more recent work on the on-going characterization of HCoV interactions with the cells from the CNS has led us to determine that two of these accessory proteins (ns2 and ns5), produced during infection of susceptible cells by HCoV-OC43, play a significant role in virulence and pathogenesis in the mouse CNS (Fig. 6) partially by modulating virus production (data not shown).

As mentioned above, SARS-CoV is also neuroinvasive and neurotropic in humans (Gu et al., 2005; Xu et al., 2005) and it could therefore be associated with the development of a neurological symptoms as infected neurons were shown to be necrotic in human brain of deceased patients (Gu et al., 2005). Furthermore, the involvement of SARS-CoV in CNS infections was underscored by the findings that made use of transgenic mouse models expressing the human angiotensin-converting enzyme-2 (the cellular receptor used by SARS-CoV to infect susceptible cells). Indeed, using these mice, it was shown that SARS-CoV could invade the CNS after an intranasal infection primarily through the olfactory bulb (Netland et al., 2008) or even after an intra-peritoneal infection (Tseng et al., 2007), with concomitant neuronal loss (Netland et al., 2008; Tseng et al., 2007); a phenomenon that can eventually lead to neurological problems. To our knowledge, there exist no reports on the detection of HCoV-HKU1, HCoV-NL63 and MERS-CoV in the human CNS. On the other hand, neurological symptoms have been described in association with both HCoV-HKU1 and HCoV-NL63 (Severance et al., 2011) and a recent report, which evaluated MERS-CoV cell tropism, suggest that, among several cell lines representative of different tissues and organs, this virus seems to be able to infect the neuron-committed human cell line NT2 (Fuk-Woo Chan et al., 2013).

Based on several pieces of evidence presented herein, we hypothesize that neuroinvasive coronaviruses could participate in the damage of the human CNS as a result of misdirected host immune responses (virus-induced neuroimmunopathology) and/or viral replication, which directly induces damage to CNS cells

(virus-induced neuropathology). In acute encephalitis, viral replication occurs in the brain tissue itself, possibly causing destructive lesions of the nervous tissue (Talbot et al., 2011). As previously mentioned, chronic human neurological diseases may also be linked to viral infection. However, in several cases of these chronic diseases, it is very hard to ascertain a role for any given virus, in part due to the difficulty of establishing the time at which these viruses become involved. Also, the four Koch's postulates dictate whether a particular infectious agent causes a specific disease (Koch, 1942). However, several viral infections, especially slow viral infections related to diseases that are rare manifestations of an infection, represent situations where Koch's postulates need to be modified (Fredericks and Relman, 1996; Hill, 1965). A series of new criteria, adapted from Sir Austin Bradford Hill's for causation (Hill, 1965), was elaborated by Giovannoni and collaborators (Giovannoni et al., 2006) and should replace Koch's postulates when one wants to evaluate the relevance of any given virus in relation to, for example, MS etiology (Giovannoni et al., 2006) or any other long-term human neurological diseases potentially related to a viral infection as well, including infection by human coronaviruses.

#### 4. Conclusions

Respiratory human coronaviruses are naturally neuroinvasive and neurotropic, with potential neuropathological consequences in genetically or otherwise susceptible individuals, with or without additional environmental insults. Even though their use of the hematogenous or transneuronal route to gain access to the CNS in human beings remains to be elucidated, their presence in the human CNS is now a recognized fact. Furthermore, knowledge of mechanisms and consequences of coronavirus interactions with the nervous system is essential to better understand potentially pathological consequences and design intervention strategies that are appropriate to encephalitis or exacerbations of other types of neurological diseases for which a given virus is involved. In that regard, the Hill's criteria adapted by Giovannoni and collaborators may represent a highly relevant tool to evaluate the relevance of

human coronaviruses as a factor which will influence the development and/or exacerbation of a long-term human neurological disease potentially related to a viral infection. Therefore, collecting new epidemiological data on a larger scale is certainly warranted to establish a more solid and direct link between coronaviruses and human neurological diseases. We have already gathered important and interesting data and identified some viral and cellular factors involved in HCoV/CNS cells interactions. However, further basic research that help decipher complex underlying mechanisms involved in virus-host-cell interactions is warranted and will be instrumental to our understanding of how coronaviruses that infect human beings, given the proper susceptibility conditions and proper virus evolution and infection conditions, may induce neuronal degeneration and could participate in the induction or exacerbation of human neuropathologies.

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