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Airborne inflammatory factors: "from the nose to the brain"

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1. ABSTRACT

The intranasal pathway is a direct route of communication between the environment and the brain. This pathway is currently used for the delivery of several experimental therapeutic peptides and vaccines because it bypasses the blood brain barrier. It is also a route of entrance to the brain for several viruses and toxic substances. Airborne infectious, allergic and pollution agents are among the most common inflammatory factors which may affect brain function via the brain-nose interface. The inflammatory processes triggered in the upper respiratory tract by these agents are positioned to influence the immune response of the brain and therefore, influence its function and alter behavior. Several clinical and epidemiological studies find an association between inflammatory factors affecting the intranasal pathway and neurological disorders such as multiple sclerosis, Alzheimer and Parkinson diseases as well as mental disorders including anxiety and mood disorders. However the mechanisms of interaction between the immune response in the nasal epithelium and the brain are poorly understood. This article discusses current evidence about these mechanisms and associations with neurological and mental diseases.

2. INTRODUCTION

Diseases of the airways due to airborne inflammatory factors are highly prevalent and their incidence is increasing. The causes have been attributed to several sources including climate changes, increasing air pollution and population growth (1-5). The major sources of contamination are infectious organisms including viruses and bacteria, allergens and air pollutants. Although they produce different types of inflammatory responses, these processes have overlapping features and influence or may potentiate each other. Moreover, while these diverse etiologies differ on other features such as their mortality rate, disease progression and damage to the respiratory system, they share the characteristics of the route of exposure and massive recruitment of lymphocytes to the respiratory epithelium with the consequent production of inflammatory molecules such as cytokines and chemokines.

The present review will discuss the impact of these inflammatory processes of the airways on the brain and behavior. This is based on the direct communication that exists between the nasal epithelium and the brain and the effects on behavior produced by activation of the brain's immune response. The vast diversity of airborne inflammatory factors will be briefly presented and

summarized. Issues related with seasonality *vs* chronic exposure will be considered throughout. The distinct inflammatory processes activated by different pathogenic sources and data about their effects on the immune response of the brain will be discussed. Emerging evidence showing altered emotional responses induced by inflammation of the airways will be put forth. Finally, the implications of these processes on neurological and mental disorders will be considered.

3. THE INTRANASAL PATHWAY

The brain is protected by many barriers that prevent the free access of molecules and cells present in the systemic circulation as well as potential pathogens. One of the most important systems is the blood brain barrier BBB composed of endothelial cells sealed by tight junctions impeding the passage of cells and large molecules into the brain (6). There are few structures in the brain were the BBB is incomplete and allow contact between the main circulation and the brain. These places are known as circumventricular organs (CVOs) and function as sensory organs monitoring the status of the "internal milieu" sending that information to higher order neuronal groups (7,8). They also are the places of release of many neuroactive substances and hormones into the general circulation. Although these places may be a direct route of entry into the brain for pathogens present systemically, these pathogens have to first reach the peripheral circulation and overcome immune surveillance mechanisms. There is however a direct route of access from the external environment into the brain bypassing the systemic circulation and the BBB. The olfactory neuroepithelium is one of the places in which neurons of the central nervous system (CNS) are in direct contact with the environment, in this case the nasal cavities (9). The olfactory neurons send their axons trough perforations in the ethmoid bone called the cribriform plate making synapses into the olfactory bulbs inside the brain. This constitutes a direct pathway of communication between the brain and the nasal epithelium and a direct route of access for pathogens and molecules present in the nasal cavities. In fact, there is currently a significant amount of evidence showing how small and large molecules can access the brain from the nasal epithelium (10-12). For example, intranasal instillation of the cytokine interferon-β results in its rapid distribution in several regions of the brain following two major pathways, one corresponding to the olfactory and another to the trigeminal systems (13). In the first case, the main targets are the olfactory bulbs, olfactory nucleus, and prefrontal cortex. Additional presence of interferon-β in other regions far from the nasal cavities including the amygdala and hippocampus was also detected. The target regions in the brain for the trigeminal pathway are the brainstem including the pons and to a lesser extent the spinal cord. Similar patterns of distribution and transfer from the nasal cavities to the brain was also demonstrated for several other molecules including insulin-like growth factor I (11) nerve growth factor and vasoactive intestinal peptide (14). Two major mechanisms have been proposed for this transfer from the nasal cavities into the brain. A direct extracellular pathway through open intercellular cleft of the olfactory epithelium into the olfactory bulbs, and an intracellular pathway from the olfactory sensory neurons via anterograde transport. This transfer of molecules have been shown for the bioactive forms of these molecules as determined by the capacity to activate cellular processes in target areas (11) or to produce effects in the brain. Indeed, intranasal instillation of recombinant cytokines including IL-4, IL-6 and IL-12 have been shown to affect the course of experimentally induced neurological disorders (15-17).

Effects on brain function and behavior of molecules administered via the intranasal pathway has also been shown in humans. Insulin administered via the nasal cavities has been reported to improve memory and cognition in humans (18-20). In addition, oxytocin was shown capable of influencing endocrine and sexual function (21,22). Similarly, intranasal atrial natriuretic peptide (ANP) and growth hormone releasing hormone (GHRH) have been shown to influence the hypothalamic-pituitary adrenal (HPA)-axis in humans (23,24). Recently, it was reported that intranasal administration of testosterone increases the reactivity of the amygdala in middle-aged women to a young adult level (25).

It is known that the intranasal pathway is also an important route of entry into the brain for several neurotropic viruses including herpes simple virus (HSV) (26), influenza virus (27) mumps virus (28) measles virus (29), Borna disease virus (BDV) (30) and arenaviruses (31). The distribution in the brain of most of these viral infections also involves regions following the olfactory and trigeminal pathway (26,32,33). In summary, the intranasal pathway is a direct route of access into the brain for molecules present in the nasal epithelium and a direct route of entry for environmental pathogens such as viruses. Either of these processes produces significant changes in brain activity and capable of affecting its function and consequently affecting behavior.

4. EXPOSURE TO AIRBORNE INFLAMMATORY FACTORS

4.1. Infectious agents

Airborne viruses and bacteria are transmitted mainly by moist droplets containing virus or bacteria originated by coughing and sneezing from infected individuals. Although the distance that they can travel has been believed relatively small (few meters), studies suggest that depending on the droplet's size and climate conditions in some cases the potential range for virulent infection may be significantly bigger (34). Some reports suggest that viruses and bacteria can move considerable distances transported in dust originated from wind storms (35). Similarly, zoonotic arenaviruses such as those responsible for hemorrhagic fever and encephalitis spread significant distance from rodents to human by wind-blown dust containing the virus (36,37). This form of transmission makes airborne viruses and bacteria extremely relevant for human health from an epidemiological point of view. They are of high incidence in the population and are among the most common causes of death (5,38-44). For example,

influenza is responsible for 100 to 500 hospitalizations per every 100,000 children and persons over 65 years of age and accounts for 36,000 deaths per year in the U.S (5,40,45,46). For these reasons extensive research has been oriented in developing early detection and preventive strategies of disease epidemic and outbreak.

In addition to mortality, airborne viruses and bacteria causes significant health problems that require interventions. An estimated of 32 million adults in the US suffer from sinusitis annually resulting in about 13 million visits to a health professional (47) with an estimated cost of 2.4 billion (48). The most common causes of sinusitis are viral infections including rhinoviruses, influenza and parainfluenza that may be followed by complications with bacterial infections (49,50). More than 50% of bacterial sinusitis are caused by *Haemophilus influenzae and Streptoccocus pneumoniae* (49,50) eventually requiring the use of antibiotics.

Exposure to airborne viruses and bacteria usually fluctuates during seasons and their incidence varies year to year. Viral respiratory infections including influenza, coronaviruses and respiratory syncytial virus (RSV) are more common during winter with a peak occasionally extending to early spring (5,44,51). In addition, many studies report an association of this peak with a subsequent respiratory bacterial pneumococcal peak of infections (44,52-54). The increased incidence of respiratory viral and bacterial infectious diseases during winter time has been related to increased contact among individuals related to living conditions in cold weather. For example, mechanisms of vector transmission through sneezing and coughs will be facilitated in closed crowded environments (44). In addition, cold air and low humidity typical of winter time will affect the capacity of the respiratory epithelium to clear airborne pathogens and increase virus transmission (55). There is, however, a certain degree of variation in the peak of incidence for each pathogen reported in the referenced studies. There are also variations between the years analyzed and between cities and countries depending on the study. The temporal sequence obtained from the referenced surveys in the northern hemisphere considering the most frequent reported incidences across studies is as follows: RSV infections have been reported early in winter from November to January. Influenza has been more consistently reported between December and February. Pneumonia and pneumococcal infections follow the peak of influenza after a 2 week interval. Finally rhinovirus and coronaviruses, including the recent human version of the bird flu causing severe acute respiratory syndrome peaks during March (5,40,44,51,52).

4.2. Allergens

Exposure to airborne allergens or aeroallergens is responsible for the most common types of allergies including allergic rhinitis or hay fever, allergic asthma and allergic conjunctivitis. These diseases are highly prevalent in developed countries and their incidence has been estimated from 20 to 30 percent in adults and up to 40 percent in children (56-59). There are basically two types of aeroallergens causing respiratory allergies, indoor allergens responsible for perennial allergic rhinitis and outdoor allergens responsible for most of the cases of seasonal allergic rhinitis. Some individuals suffer from both perennial and seasonal allergic rhinitis and a similar situation is often found for allergic asthma as well. The most common indoor aeroallergens are dust mite, mold, animal dander and cockroach parts while the most prevalent outdoor aeroallergens are pollen and spores (60). In susceptible individuals that are prone for the development of allergies, repeated exposure to any of these allergens may result in sensitization and development of respiratory allergies. Allergic rhinitis accounts for approximately 70% of all cases of allergies and is also linked to the development of allergic asthma. The burden caused by these diseases is costly for society and bothersome to individuals suffering from respiratory allergies causing impairments in daily functioning and quality of life (56-59).

Exposure to airborne allergens may occur chronically depending on housing conditions such as the case of perennial aeroallergens and may lead to chronic allergic disorders. Outdoor aeroallergens are mostly of seasonal nature with a high incidence in specific times of the year such as spring (tree pollen) and fall (weed pollen). One of the most dramatic seasonal changes in incidence of upper respiratory inflammatory disease is represented by the robust increase in pollen-induced allergy during spring (61). Pollen represents the most important and the most seasonal among aeroallergens (http://www.aaaai.org/nab/index.cfm). While pollen levels are detectable throughout the year, they are usually below 100 grains/cubic meter which are the level below the majority of susceptible allergic humans do not report symptoms (61). For example, a study analyzing weekly mean values for total pollen production in the Washington-Baltimore area reported an increase form less than 100 grains/cubic meter to about 400 grains/cubic meter during the first week of April followed by an increase to more than 1000 to 1,300 grains cubic/meter in the second to third week of April (62). The levels of pollen return to below 100 grains/cubic meter by the first week of June. Allergies to pollen represent the most important cause of seasonal allergic rhinitis and inflammatory complications of the respiratory system. It has been reported that individuals suffering from allergic rhinitis are more likely to suffer from bacterial and viral complications of the sinuses and upper respiratory tract and that a history of viral infections worsens the symptoms of allergies (63-66). Thus, respiratory allergies caused by aeroallergens are highly prevalent and viral and bacterial infections more common in people suffering from allergies.

4.3. Pollutants

Exposure to air pollutants is an increasing problem in industrialized countries and is believed to impose a serious health problem in urban populations. The most common air pollutants are particulate matter (PM) of different sizes originated from different sources including power plants, motor vehicles, construction sites, deforestation and industrialization processes (2,49). The most dangerous for human health are fine sizes particles up

to 2.5 microns ($PM_{2.5}$) that can be suspended in the air for large periods of time and transported long distances by wind and climatic variables (4). Among the most problematic are fine carbon particles originated mainly from motor vehicles using diesel fuel. They have been associated with increased mortality rate due to respiratory and cardiovascular diseases believed to be produced or worsened by increased exposure to particulate matter (2,67-69). In addition, several epidemiological studies report the association between diesel exhaust particles and increased incidence or respiratory diseases such as bronchitis and asthma (3,70,71). Perhaps the most remarkable and controversial series of studies are those relating the increase incidence of asthma in Caribbean countries due to dust containing coarse particulate matter (less than 10 microns) originated in the Sahara desert (72,73). Although more research is needed to confirm this association, these studies signify the potential of range of exposure and health hazard that particulate matter has in the world.

Another feature of PM is that they may interact with others pathogens and serve as transporters of viruses, bacteria or molecules with infectious or antigenic properties such as cell walls of bacteria (35). For instance, PM containing bacterial lipopolysaccharides (LPS) has been associated with the development of respiratory diseases and is believed an important occupational hazard (69,74,75). Moreover, the combination of pollen with diesel exhaust particles is believed to increase the occurrence of asthma and the aggravation of symptoms in asthmatics (3).

The pattern of exposure to PM depends from the distance of the sources and the interaction of PM with atmospheric variables including (but not limited to) winds, humidity, precipitations and temperature. In some cases, a seasonal pattern of exposure has been observed for certain PM depending on seasonal weather conditions such as high pressure systems and rainfall (4). Because of the increasing sources of PM, their capacity to reach long distances and ability to serve as "carriers" of other inflammatory and pathogenic factors, PM is a significant airborne inflammatory factor of increasing importance across the world.

5. NEUROIMMUNE PROCESSES TRIGGERED BY AIRBORNE INFLAMMATORY FACTORS

Airborne inflammatory factors including viruses, bacteria, allergens and pollutants have the potential to affect brain function and behavior by two major mechanisms. In the case of infectious agents such as viruses and bacteria one mechanism is by accessing the brain and establishing acute and/or permanent infections. The second mechanism is by inducing an inflammatory process in the respiratory epithelium, in particular the upper respiratory tract, produced in response to non-invading inflammatory factors such as infectious agents, allergens and pollutants. The first case conveys the most dramatic outcomes in which some airborne viruses and bacteria may produce major neurological and systemic symptoms. They also may result in death by meningitis or encephalitis or sub-lethal infections with significant cell loss and neurological sequelae. The second case involves exposure to the most common and prevalent types of viral and bacterial infections, allergens and air pollutants activating an inflammatory response in the upper respiratory epithelium that may interfere with the functioning of certain areas of the brain.

5.1. Invasion of the brain

Several types of airborne viruses including influenza, measles and mumps and others such herpes simple viruses may access the brain from the nasal cavities and produce meningitis and/or meningoencephalitis (27,76-79). Similarly, airborne bacteria including *Neisseria menigitidis, Haemophilus influenza* and *Streptococcus pneumoniae* establish infections in the nasopharinx that can spread to the meningeal spaces causing more serious types of meningitis (42,80). The course of these illnesses, treatment and mechanisms of brain damage of these infectious pathogens has been largely studied and there is today significant available information on the effects of acute meningitis and encephalitis (76,79-85). Among the best known effects are the massive recruitment of lymphocytes to the menigeal spaces and production of inflammatory molecules usually resulting in edema formation and intracranial hemorrhage (42). The neurological consequences of these processes depends on the brain region affected and range from loss of function such as impairment in vision and/or the development of seizures (42,81,82,86).

Inflammatory mechanisms of the brain's immunity have a deep impact on brain function with variable outcomes for survivors. One of the most important is the massive production of cytokines, chemokines and reactive oxygen species, mostly by microglial cells of the brain parenchyma, that produce important alterations and/or damage to neurons and nerve cells (85,87-90). The presence of toll-like receptors in glial cells allows the detection of bacterial and viral products which triggers the production of a common set of cytokines including interleukin-1β, interleukin-6, tumor necrosis factor-alpha and additionally interferons in the case of viral infections (30,83,84,90-92). The effect that these cytokines may produce in the brain varies according to the intensity of the response as well as the developmental stage of the infected organism. Cytokines at high concentration are cytotoxic and may trigger neuronal cell death by necrosis or apoptosis and that may result in the loss of some function depending on the region affected (84,92,93). Moreover, if the infections occur during early development of the nervous system, they are likely to cause permanent alteration in brain function. In this case, it may not only involve loss of function but also subtle alterations in information processing (94-96). Cytokines have important neurodevelopmental functions and alteration in their expression may have important effects on brain function (97). Indeed, experimental models of maternal and neonatal influenza or BVD infection in rodents show the damaging long-term consequences on memory function and other behavioral traits (98-100).

Airborne neurotropic arenaviruses are less common and limited to endemic regions, mostly in Africa and South America. However, the mortality rate is high ranging between 15 to 35 % (36,37,101,102). These viruses are capable of accessing the brain parenchyma trough the olfactory and trigeminal pathway causing viral encephalitis (31,32,103). Their clinical course is characterized by neurological disorders including ataxia, tremors and seizures. The long term consequences in survivors are neurological disabilities and psychiatric disorders including impaired cognitive abilities and depression (32). Recent data indicates that immune mechanisms of pathogen clearance are mayor players in inducing neuronal loss and apoptosis. Recent data provided by experimental animal models of neonatal arenavirus infections via the intranasal pathway shows that the immune response has a greater role in the process of encephalitis than the virus itself (32). Infected mice deficient in T-cells had a reduced production of interferon-γ and TNF-α but a 100% survival and equal viral load in the brain to that of wild type mice (32). In addition, neutralization of TNF-α with antibodies also protected new born mice from the arenavirus encephalitis (32).

Some viruses may also access the brain by the intranasal pathway although their airborne status is less common or documented. Borna disease virus (BDV) (30,96,104-106) and herpes simplex virus-1 (HSV-1) (26,106-109) have been shown to access the brain through the intranasal pathway following olfactory and trigeminal routes and establish acute and/or permanent slow infections. Permanent asymptomatic infections may affect brain function by mechanisms that interfere with neuronal processes. Experimental models of neonatal BVD infection have shown that asymptomatic BVD infections interfere with several neuronal intracellular processes involving kinases (110-112). The dysfunction in kinase activity and interference with cell-signaling caused by the virus has been related with impaired memory function (108,113).

In summary, airborne infectious agents may access the brain through the intranasal pathway and are potent activators of the immune response of the brain that may lead to neuronal damage and long-term functional sequelae.

5.2. Inflammation in the nasal and respiratory epithelium

The most common and prevalent types of airborne inflammatory factors do not enter the brain, however they produces significant inflammatory processes in the respiratory system and in particular the nasal cavities, nasal sinuses and nasopharinx. Viruses such as influenza induce the activation of the innate immune response in respiratory epithelial cells and the production of type I interferons that initiate the antiviral response (114). Adaptive immune processes involving activation and recruitment of T- lymphocytes and later antibody production are mostly responsible for viral clearance (115,116). Experimental animal models of influenza infection show that the virus induces significant apoptosis in olfactory neurons and that this is a mechanism prevents invasion of the brain (117). On the other side, rhinoviruses causing the common cold do not induce a strong interferon response (118,119) but produces significant inflammation of the upper respiratory tract and the induction of TNF-α, interleukin-6 and the chemokines interleukin-8 and RANTES (120). Prolonged inflammatory responses caused by rhinovirus have been associated with increased susceptibility to bacterial infections (121). Bacterial complications of the sinus such as infections with nontypeable *Haemophilus influenza* are characterized by the production of several cytokines including TNF-α, interleukin-1β and interleukin-6 and the presence of several types of T lymphocytes (117,121-124). All together, these inflammatory pathogens produce significant changes in the immunity of the respiratory system and the type of response mounted after successive infections (125-127).

Allergic inflammation is characterized by a massive recruitment of type 2 (T_H2) T-lymphocytes into the nasal epithelium and the production of the cytokines IL-4, IL-5 and IL-13 (60). In individuals with respiratory allergies, the cytokine response of T-cells is biased towards a T_H2 type characterized by the production of IL-4, IL-5 and IL-13 (128). This T_H2 biased response drives isotype switching towards the production of IgE, which in turn, sensitizes mast cells to respond to environmental stimuli. Mast cells are resident immune cells involved in many types of defense mechanisms against pathogens and are instrumental in the antibacterial, anti-parasitic and allergic responses. Mast cells are the first responder to pathogens and allergens in the nasal cavity and are involved in both innate and adaptive immune responses (60,129-131). They constitutively and upon activation produce several cytokines including IL-5, IL-13 and TNF-α, and massively release them during degranulation. Moreover, they release several neurotransmitter and inflammatory mediators such as histamine, leukotrienes and proteases responsible for the nasal symptoms of allergies. T-lymphocytes (T-cells) are also important source of T_H2 cytokines in the nasal epithelium (in particular IL-4 and IL-13) during allergic processes (60,130). Although their presence and production of cytokines is limited during early stages of allergic responses, their number and activity increases rapidly thereafter becoming perhaps the major producers of IL-4 and IL-13 during allergic inflammation. Eosinophils and basophils also contribute significantly to the production of cytokines including IL-5 and IL-13 and other immune mediators such as proteases and leukotrienes. A growing number of cytokines have been shown produced and released during allergic inflammation including IL-3, IL-9 and IL-17 with relatively lower titers with respect to those of IL-4, IL-5 and IL-13. Repeated and chronic exposure to allergens may lead to chronic allergic inflammation characterized by significant tissue damage and remodeling with a consequent decline in function.

Pollutants may induce either a pro-inflammatory response in the nasal epithelium or exacerbate allergic inflammatory processes. Most animal models showed pro-inflammatory processes with the production of TNF-α that were induced in response to several contaminants such as carbon ultrafine particles (132-134). On the other hand, the combination of diesel-exhaust particles or particulate

matter with pollen increases specific IgE antibody responses against pollen (135) and IL-4 production (136) resulting in the amplification of allergic inflammation. Therefore, pollutants generally induce a pro-inflammatory response when acting alone or may serve as adjuvant of allergic inflammation when combined with allergens.

Although the inflammatory process and the production of cytokine described above are mainly restricted to the nasal and respiratory epithelium, recent experiments from our laboratory showed that inflammation in the nasal cavities is a stimulus capable of inducing cytokine production in the brain (137). Intranasal administration of bacterial products such as LPS resulted in the expression of the cytokines TNF-α and IL-6 in the brainstem and hippocampus of rats. These effects were more pronounced in females as compared to males and simultaneous whit the development of depressive-like behavior (see next section). Similarly, studies from other laboratories on experimental animal models showed that exposure to PM are capable of inducing cytokine expression in the brain of mice (134,138). Ultrafine carbon particles intranasally instilled or aerosolized induced the expression of IL-1α and β, TNF-α and several chemokines including MIP-1α and CXCL9 (134,138). Recently, it has been shown that exposure to PM increased the levels of glial fibrillary acid protein (GFAP) and produced activation of the transcription factors NF-kappa B and AP-1 in the brain (133). Furthermore, intranasal instillations with polyinosinic:polycytidylic acid (poly I:C) that mimics immune processes triggered by viruses were shown to induce cytokine expression in the brain (139). Together, these studies show that bacterial, viral and pollutant products administered in the nasal cavities induces activation of the immune response inside the brain probably reflecting inflammation in the nasal cavities.

Allergic inflammatory processes of the airways such as allergic rhinitis and allergic asthma have been shown to affect brain function (140-143). Exposure to the allergen in sensitized rodents is also capable of inducing the expression of cytokines in the brain. Data from experimentally-induced allergic rhinitis in rats showed that the cytokines IL-4, 5 and 13 are induced in the prefrontal cortex and olfactory bulbs of rats made allergic to tree pollen (144). Expression of these cytokines in the same brain regions were also observed in mice with experimentally-induced allergic rhinitis to albumin from chicken egg (OVA) (144). Moreover, neuronal activation of limbic regions was reported in models of allergic asthma in OVA-sensitized mice intranasally challenged with the allergen (141,142). Using the expression of c-fos as a marker of neuronal activation, several responsive areas in the brain including the amygdala and hypothalamus were observed during allergic processes of the airways (141,142). These studies show that airborne allergies are capable of affecting the brain inducing the expression of T_H2 cytokines and producing the activation of several brain regions.

In summary, data from different sources shows that intranasal immune challenge resulting in distinct inflammatory processes of the nasal epithelium is a stimulus capable of activating at least the molecular inflammatory response of the brain.

6. EFFECTS ON BEHAVIOR

6.1. Acute Infections

As discussed earlier, the effects on brain function and behavior of acute meningitis or encephalitis has been extensively studied. The most important consequences are loss of function such as impaired vision and hearing, movement disorders or ataxia and seizures (76,80). Survivors of bacterial or viral meningitis or encephalitis usually present alterations in behavior that relates to the degree of damage caused during the acute phase. Despite extensive research in this subject, the mechanisms on how brain function and behavior are affected after viral clearance and resolution of symptoms are only partially understood (145). Depression, anxiety and cognitive impairments have been described in survivors of acute encephalitis (145). Experimental animal models of prenatal infection with influenza virus reveal the important role that the immune response has on neurodevelopment (76,80,97,99,146). Infections with influenza virus in pregnant dams results in neurological and behavioral alterations in the offspring (97-99,146). The offspring of mice infected during pregnancy display deficits in exploratory behavior, social interaction and recognition of novel objects (99). Moreover, specific deficits in acoustic startle responses similar to those observed in humans with schizophrenia were also reported (99).These studies determined that the virus was not present in the fetus and that the effects on the brain and behavior are likely related to the activation of the maternal immune response. These findings have led to the hypothesis of a maternal immune activation as a possible etiology for cases of schizophrenia (98,99).

6.2. Permanent infections

Permanent infections or slow viral infections of the CNS such as those established by BDV and HSV virus have been strongly implicated with impairment in learning and memory function (96,112,113). For instance, using models of neonatal BVD infection it is possible to detect a progressive impairment in the performance of rats in the Morris Water Maze test (96). This test is usually employed to assess spatial learning and memory function. When BVD infected animals were evaluated for ambulatory activity in an open field, no signs of altered behavior was observed (113) showing that only specific behavioral alterations were caused by the virus. Many of the behavioral effects of permanent or slow BVD infection may not involve activation of the cytokine response of the brain (113). This may be related with mechanism of evasion from immune surveillance and the ability of BDV to establish permanent infections (147). BVD usually affects the hippocampus and cerebral cortex, regions known to process several aspects of memory function (111,148). Using cell culture systems it has been shown that BVD blocks potentiation of synaptic activity of neurons that is believed a neuronal process associated with memory formation and consolidation (110). Moreover, the effects of BVD infection in neurons seem to

be specific for activity dependent changes in synaptic function without affecting other electrical properties (112). These effects relates with the interference of BVD virus of several intracellular phosphorylation processes required for synaptic plasticity.

6.3. Inflammation in the airways

It is known that activation of the peripheral immune response produces behavioral responses of depression and anxiety (149-151). Some features of depressed patients including anhedonia, loss of appetite, sleep disturbances and reduced general activity are similar to the behavioral symptoms of sickness behavior. This has led to hypothesize that the high incidence of mood and anxiety disorders in clinically ill people stems from an immune or neuroimmune origin (149,151,152).

During inflammatory processes, depression and anxiety in humans and depressive-like and anxiety-like behaviors in animals have been shown associated or mediated by the actions of a specific subset of pro-inflammatory cytokines including interleukin-1β (IL-1β) IL-2, IL-6, and tumor necrosis factor- α (TNF-α) and the antiviral cytokines interferons α, β and γ (149-151,153,154). Interferons and IL-2 have been shown to promote depression mainly by acting in the periphery by mechanisms involving the enzyme indolamine 2,3 dyoxigenase (IDO) (149). IL-1β, IL-6 and TNF-α have been shown to influence depression by peripheral mechanisms and by direct central actions in the CNS (149,154). Central mechanisms of these cytokines involve activation of the HPA-axis and a reduction in neurogenesis. We have also proposed that behaviors of depression and anxiety may result by direct actions of these cytokines at the synaptic level by reducing synaptic plasticity (155).

One known mechanisms of the immune response of the brain is the induction of inflammatory genes in response to peripheral immune challenge (152,155-158).Thus, inflammatory processes of the airways that may result in the expression of cytokines in the brain may result in altered behavioral responses. Indeed, intranasal administration of bacterial LPS in rats induced depressive-like behavior and exaggerated hormonal responses to stress without any overt sign of sickness (137). Rats administered for 2 consecutive days in the nasal cavities with bacterial LPS had reduced swimming time in the forced swim test which is indicative of behavioral despair. These effects were paralleled by the expression of TNF-α and IL-6 in the brain. Although it has not been determined if the depressive-like behavior was produced by the expression of the cytokines in the brain, it is likely that the may play a contributing role for the manifestation of depressive-like behavior. These studies were intended to mimic the activation of the immune system due to a gram negative bacterial infection in the nasal cavities. However, it may also represent inflammatory processes triggered by PM containing LPS.

Similarly, allergic inflammatory processes of the airways have been shown to induce anxiety-like behaviors. Animals sensitized and exposed to an allergen shows increased anxiety-like behavior as determined by the elevated plus maze test and the open field test (144). Allergic mice spend less time in the open arms of an elevated plus maze or in the center area of an open field which are considered measures of increased anxiety. Moreover, evidence of increased anxiety caused by aerosol challenge with allergen was obtained using a modified version of the passive avoidance test (142). Mice that were sensitized and then exposed to an allergen in a compartment showed avoidance to that compartment when re-exposed a day later in the absence of the allergen. Thus, allergic mice developed an aversion to the context in which the allergic reaction occurred suggesting that neuroimmune mechanisms were capable of behaviorally conditioning allergic mice (142).

7. IMPLICATIONS FOR NEUROLOGICAL AND MENTAL DISEASES

It has been hypothesized that neurological and mental disorders of unknown etiology may have an infectious or immunological origin (98,100,159). The data supporting an inflammatory component originates from epidemiological, clinical, postmortem and basic animal models. However, attempts to evaluate and establish a direct relationship between these disorders and specific infectious agents or inflammatory diseases have been elusive. In this regard, it has to be considered that while studies exist that lead to these hypotheses, this area of research is on its beginning. Moreover, taking into account the likelihood that the clinical manifestation of a specific neurological or mental disorder may originate from different etiologies, attempts to relate complex disorders of the brain to a single infectious or inflammatory source are likely to produce mixed or inconclusive results. Recently, evidence of the presence of a specific infectious agent associated with a specific disease started to emerge supporting the more indirect epidemiological analysis encountered often in the literature. Together with cases of effectiveness of response to treatment using immunomodulatory drugs, we will briefly present some of the evidence suggesting a relationship between some neurological and mental disorders with immune mediated processes affecting the brain involving the intranasal pathway and possibly airborne exposure to inflammatory factors.

7.1. Neurological disorders

Alzheimer's disease (AD), multiple sclerosis (MS) and Parkinson's disease (PD) have been proposed to have an inflammatory etiology or at least, that inflammatory processes are a contributing factor or a factor of risk (98,160-166). In the case of AD and MS, specific viruses have been studied in association with these diseases while PD has been associated with exposure to environmental toxins and the occurrence of rhinorrhea. Perhaps, the most compelling evidence for an association between a neurological disorder and a virus is the case of MS (167-172). Human Herpes viruses (HHVs) have been found with more frequency in MS patients with respect to other neurological diseases and controls. Varicella zoster virus (HHV-3), Epstein-Barr virus (HHV-4) and HHV-6 in

conjunction with a strong T-cell responses against these viruses have been consistently found in MS patients (168,171-176). With the exception of HHV-6 which an airborne transmission is not known, HHV-3 and HHV-4 can be transmitted by moist droplets containing the virus and infect the nasopharinx and also display neurotrophism accessing the brain via the intranasal pathway. Measles virus has also been associated with MS and a similar body of evidence supports a role of measles virus with MS (164,172). Evidence of antibody titers against measles virus in the cerebrospinal fluid of MS patients has been reported (172). Also, epidemiological evidence of an association between MS and measles virus is available (164). Other than the form of transmission, the initial infection site in the nasopharinx and access to the brain via the intranasal pathway, these two groups of viruses do not share many similarities.

The pattern of functional loss and degeneration from the olfactory sensory group in both AD and PD has lead to the olfactory degenerative hypothesis for these diseases (159,177-179). In these cases, a causative environmental factor is assumed to initiate in the olfactory bulbs the series of neurological alterations that lead to the progressive degeneration along the olfactory pathway. In the case of AD, one of such potential factors is herpes simplex virus type 1 (HSV-1) (160,161,165,180-183). Although the occurrence of aerosolized HSV-1 infection is rare, there is evidence that the spread of infection to the brain occurs trough the intranasal pathway (26,33,139,184). Experimental animal models of intranasal HSV virus infection shows that the virus spreads through the olfactory pathway reaching the limbic regions where degeneration occurs in AD. Amyloid deposition in neurons in response to HSV infection has also been demonstrated using cell culture (182). Data demonstrating the presence of HSV virus in the amyloid plaques of AD patients was reported by two studies (180,183). These studies also reported that the interaction between genetic susceptibility for amyloid deposition and a viral presence was associated with increased neurodegeneration.

The evidence of a viral involvement in PD is only circumstantial and limited (185). However, epidemiological data points to a different inflammatory process to that of viral or bacterial infections. Studies have reported increased susceptibility for PD associated with exposure to environmental contaminants and in particular with pesticides (165,180,183,186). In addition to these factors, PD has been associated with the presence of rhinorrhea and immediate-hypersensitive reactions (187). These studies suggest that inflammatory processes in the nasal epithelium may be of importance if there is in fact a relationship between PD and environmental contaminants. In this regard, an involvement of inflammatory processes in PD has been demonstrated by the presence of elevated cytokines in the brain of PD patients and in animal models of PD (166,188,189). This is corroborated by the protection to PD conferred by the use of anti-inflammatory drugs and the reductions of symptoms in animal models (190,191). Furthermore, specific markers of the adaptive immunity involving T-lymphocytes have been found in the brain of postmortem PD patients and in animal models of PD (192).

While the type of inflammatory agent or pathogen that has been associated with these diseases differs, the unifying point that represents the route of exposure involving inflammatory processes initiated in the nasal epithelium and regions of the brain affected in relation with the intranasal pathway highlights the potential role of neuroimmune mechanisms at the environment-brain interface. If research continues to produce evidence of an inflammatory role in these diseases for airborne infectious, toxic and allergic factors, understanding of neuroimmune mechanisms of the intra nasal pathway will be crucial for a better approach for the prevention and treatment of these diseases.

7.2. Mental Disorders

The concept that immune function may play a role in mental illness and in particular depression has been reviewed several times (149,193-196). The concept has been built based on several lines of evidence including a) depression and anxiety occurring in a large number of patients receiving cytokine therapy for hepatitis-C or melanoma (197) b) the presence of markers of inflammation in depressed patient and the normalization after antidepressant treatment (198) c) the occurrence of depression in autoimmune and chronically ill patients (199) d) animal studies showing that challenge with bacterial and viral products as well as cytokines induces features of depressive-like behavior (149,150,193). There is today general consensus on some mechanisms of neuroimmune interaction that leads to the occurrence or worsening of depression (see section 6.2). However, the possibility that mood disorders and other psychiatry diseases may be related (at least in part) with inflammatory processes involving the intranasal pathway has never been considered. One observation in favor of this connection is that the most consistent findings of anomalies in the brain of patients with mood disorders and animal models of depression involve the fronto-temporal regions (200). The frontal cortex and hippocampus that are regions closely related with the intranasal pathway consistently show neurochemical and cellular alterations that reflects in functional deficits in mood disorders patients (200-203). A genetic predisposition and exposure to stress have been identified as the major contributors to alterations on these brain regions. Specifically, the role of the stress response and the effects of glucocorticoids on brain architecture and neurochemistry are proposed as a major mechanism leading to the neuropathology of mood disorders in fronto-temporal regions (200). While inflammatory processes of the airways and the intranasal pathway are unlikely to be the cause of these neurochemical alterations and the development of depression, they are positioned to greatly influence its outcome. We have recently shown that in rats, sub-syndromal inflammatory processes of the airway mimicking bacterial or toxic exposure are capable of enhancing the glucocrticoid response to stress (137). Moreover, they were capable of inducing transcription of pro-inflammatory cytokines in the hippocampus. The simultaneous effects of cytokines in the brain with increased hormonal responses to stress are likely to result in increased deleterious effects to a stressor on hippocampal neurons.

Epidemiological and clinical studies report a higher incidence of depression and anxiety in individuals suffering from respiratory allergies including allergic rhinitis and allergic asthma (56,204-212). Increased state and trait anxiety were identified using the state and trait anxiety inventory (STAI) in individuals suffering from allergic rhinitis compared with matched controls (208). These findings were recently replicated by an independent study including atopic dermatitis and seasonal allergic rhinitis with the use of the STAI (209). Comparisons of allergic *vs* non-allergic asthmatic patients revealed and association with anxiety only for allergic asthmatics independent of age, sex, smoking status and asthma severity (210). This study adds evidence for a role of allergies to the vast literature reporting increased anxiety in asthmatic patients (206,211,213). As discussed in section 6.2, experimentally induced allergic rhinitis and asthma in rodents induces anxiety-like behavior, yet the mechanisms linking respiratory allergies with anxiety and depression are poorly understood.

It has been recently hypothesized that a changing microbial environment is responsible for a faulty mechanism of the immune response in terminating inflammatory processes (214). This has been related with the increased incidence of chronic inflammatory diseases in developed countries such as allergic rhinitis and asthma, type I diabetes and MS and inflammatory bowel diseases among others (214,215). The so-called "hygiene hypothesis" or "old friends hypothesis" has been recently proposed in relation with the increased incidence of psychiatric diseases, in particular anxiety and mood disorders (216). Rook and Lowry proposes that a low ratio of regulatory to effector T cells possibly related with diminished harmless organisms and almost absent parasitic Helminth infections in developed countries is the cause of the high incidence of chronic inflammatory diseases. Moreover, the authors propose that T_H1- driven chronic inflammatory processes and the production of IFNγ will be associated with increased incidence of depression in individuals with autoimmune diseases. Conversely, T_H2-driven chronic inflammatory processes and the production of IL-4, 5 and 13 will be associated with a higher incidence of anxiety disorders in allergic individuals. In relation with inflammatory processes of the airways, this view is consistent with our findings that intranasal immune challenge with LPS induces depressive-like behavior (137) and that intranasal challenge with allergens induces anxiety-like behavior (144).

In summary, activation of the immune system and elevation in cytokines has been shown to promote depression and anxiety. The high rate of exposure to airborne inflammatory factors and the characteristics of the intranasal pathway may play a contributing role by triggering, worsening or perpetuating mood and anxiety disorders.

8. SUMMARY AND PERSPECTIVES

The concept that infectious diseases may play a role in neurological and mental disorders has been proposed several times, nevertheless studies have produced mixed results and conclusive evidence is still lacking. New evidence linking infectious agents with diseases of the brain have emerged recently and this subject of research may continue to provide information about a potential environmental role on neurological and mental disorders. However, it is acknowledged that these diseases are highly heterogeneous on their clinical manifestations and that they may result from the interaction between genetic susceptibility and several environmental variables. Therefore, if there is an inflammatory origin in the etiology of any of these disorders, it is likely that more than one single infectious or inflammatory environmental factor is involved and capable of producing a group of symptoms leading to a specific clinical manifestation. We have proposed that the intranasal pathway represents one unifying mechanism by which environmental inflammatory factors may initiate, maintain or influence the progression of neurological and mental disorders. The constant or repetitive nature of exposure to airborne inflammatory factors that covers the lifespan of an individual may play an important role in the magnitude of the inflammatory response mounted by the brain. Importantly, we suggest that these inflammatory factors influence each other as evidenced by the increased co-occurrence of infectious and allergic diseases and the link between air pollution and airway inflammation. Potential neuroimmune mechanisms at the nasal epithelium and activation of the immune response of the brain are likely candidates to affect specific brain-regions related with the intranasal pathway involving the olfactory-fronto-temporal regions and the trigeminal target areas. However, these mechanisms have to be yet characterized and explored in more detail to understand how exposure of environmental inflammatory factors may play a role in brain function and disease.

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