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Neural dysfunction following respiratory viral infection as a cause of chronic cough hypersensitivity

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Abstract

Respiratory viral infections are a common cause of acute coughing, an irritating symptom for the patient and an important mechanism of transmission for the virus. Although poorly described, the inflammatory consequences of infection likely induce coughing by chemical (inflammatory mediator) or mechanical (mucous) activation of the cough-evoking sensory nerves that innervate the airway wall. For some individuals, acute cough can evolve into a chronic condition, in which cough and aberrant airway sensations long outlast the initial viral infection. This suggests that some viruses have the capacity to induce persistent plasticity in the neural pathways mediating cough. In this brief review we present the clinical evidence of acute and chronic neural dysfunction following viral respiratory tract infections and explore possible mechanisms by which the nervous system may undergo activation, sensitization and plasticity.

Keywords

Peripheral sensitization; Central sensitization; Rhinovirus; Neural plasticity

1. Introduction

Contributing to the persistence of many respiratory viral strains is the evolutionary mutation and selection that renders them capable of exiting the host to infect others. This transmissibility is accomplished by altering the function of the nervous system. In the nasal

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airways, viral induced alterations in neurophysiology leads to sneezing and parasympathetic reflex secretions while in the trachea/bronchi it leads to coughing, parasympathetic reflex secretions and bronchoconstriction. Although little more than an inconvenience for some, this neuromodulation likely contributes to viral associated exacerbations of disease in those with reactive airways disorders. In addition, the neuromodulation may outlive the viral infection and cause persistent symptoms in some individuals. This is most noted for the viral-induced cough that can persist well beyond the time needed for immunological clearance of the viral infection. By altering the nervous system, respiratory viruses may succeed in escaping, but often leave behind a host with excessive cough and/or exacerbated respiratory disease. In this brief review we summarize the mechanisms regulating viral induced neuromodulation and describe the clinical data that support the notion of respiratory viral induced sensory dysfunction in human respiratory morbidity.

2. Virus Infection and the Clinical Manifestation of Cough

A cough which follows a viral respiratory tract infection is typically self-limiting, lasting no more than a couple of weeks (Ebell et al 2013; Pratter, 1996). Symptom duration is used clinically to distinguish an ‘acute’ cough resolving within three weeks from one considered to be ‘chronic’ and which somewhat arbitrarily is defined as lasting longer than eight weeks (Irwin, 2006; Morice et al 2006). Despite the transient and relatively innocuous nature of an acute viral cough the vast numbers of otherwise healthy individuals ‘smitten’ during the autumn and winter combined with the disruptive nature of the cough help to explain why many billions of dollars of over the counter (OTC) cough remedies are purchased worldwide each year (Fendrick et al. 2003). As alluded to above not all post viral cough is short-lived and many patients attending specialist cough clinics report an initiating ‘viral infection’ months and in many cases years before they seek specialist help (Haque et al. 2005). Viruses therefore initially alter the cough reflex which may be initially beneficial for airway clearance but the effects can persist long after the infection has resolved leaving the host with an abnormally sensitive airway which manifests clinically as troublesome bouts of cough triggered by exposure to low level physical and chemical stimuli (McGarvey et al. 2009). Exactly how infection alters neuronal function is unclear and much of the work undertaken to elucidate the mechanisms responsible has been undertaken in animal studies and *in vitro* cell based experiments. However there is a sizeable literature of studies designed to shed light on the relationship between respiratory infection and cough that have been conducted in human subjects. The vast majority have been concerned with viral respiratory tract infection and some of these will be considered in more detail in this review.

Viral associated cough can be investigated in humans within the context of naturally occurring infection. The types of studies undertaken range from questionnaire based consumer surveys often sponsored by the OTC industry to more detailed epidemiological studies where the aetiology of the infection has been identified the clinical characteristics of the infected population recorded and the symptomatic course of the infection followed from its onset through to the natural resolution. In the Attitudes of Consumers Toward Health, Cough, and Cold (ACHOO) survey, undertaken in a population of over 3000 randomly selected internet/online device users, the ‘cold’ was common occurring in 85% of respondents at least once in the previous year (Blaiss et al. 2015) A sore or ‘scratchy’ throat

often heralded the onset but cough, the most symptom, was present 75% of the time and typically occurred 1–5 days after onset of the ‘cold’. In over a third it lasted more than a week. It is notable that epidemiological studies of naturally occurring infection in the general population have reported similar findings to the consumer surveys. For example in one study of young adults who developed a respiratory illness, cough among other symptoms was more common in those culturing rhinovirus and although the median illness duration was approximately 7 days about 25% were still symptomatic at two weeks (Gwaltney et al 1967). In the 1950’s Jackson and colleagues undertook observations in more than 1000 volunteers who they had challenged with infectious nasal secretions from a donor with symptoms of a typical common cold. They recorded the clinical features and designed an objective scoring tool based on symptoms and using this scoring scale developed criteria to diagnose a ‘cold’ in experimental conditions (Jackson et al. 1958). Other tools such as the Wisconsin Upper Respiratory Symptom Survey (WURSS) have since been developed and validated in naturally occurring colds (Barrett et al 2009). Although both measure cough as a distinct ‘symptom’ item there is no agreement as to which most accurately captures the clinical impact of cough or correlates best with alteration in airway function and inflammation.

Inhaled tussive agents such as citric acid and capsaicin evoke cough in a dose dependent manner and are widely used as an experimental tool to study cough reflex sensitivity (Morice et al. 2007). In a prospective study of healthy volunteers studied at baseline, during and after a naturally acquired upper respiratory tract infection (of presumed viral origin), O’Connell *et al* observed an increase in capsaicin cough sensitivity during the infection which reduced to baseline levels at recovery (O’Connell et al. 1994). This finding was confined mainly to those reporting a dry cough rather than a productive one or those with no cough. Increased cough responses to mechanical stimuli (such as that delivered by a commercial percussion device applied to the chest wall) and a heightened sensory awareness of a need or ‘urge to cough’ have also been observed during viral infection suggest there is a complex and polymodal sensory neural modulation in response to viral infection (Dicpinigaitis et al. 2011; Eccles et al. 2004). While these experiments have provided clinical evidence of virus induced cough hypersensitivity they provide little mechanistic insight into the observation. To gain deeper understanding into how respiratory infection alters the human cough reflex in vivo studies of experimentally induced respiratory tract infections have been conducted.

Human rhinovirus (HRV) accounts for 30–50% of all acute respiratory illnesses (Gwaltney et al. 1966; Turner 1997; Zambon et al. 2001) and is a common cause of asthma and COPD exacerbations (Mallia et al. 2006). As a consequence most of what is currently known regarding the pathophysiological mechanisms of viral induced airways disease has involved the study of human subjects experimentally infected with HRV. Surprisingly there has been no work undertaken to specifically study the *in vivo* effect of viruses on the human cough reflex. Following intranasal challenge 95% of individuals without antibodies against the specific viral serotype will be infected although only three quarters will develop a clinical infection. Cough may only be present in 30% of infected individuals (Tyrrell et al. 1993) which contrasts the higher prevalence of cough reported by patients with naturally occurring

colds (Butler et al. 2002). In those with clinical symptoms rhinovirus is often recovered from the lower airway (Gern et al. 1997; Halperin et al. 1983). Although the airway epithelial cells are the key site for viral replication, infection does not cause a marked cytopathic effect. Binding to its receptor, intercellular adhesion molecule 1 (ICAM 1), on airway cells does trigger the release of inflammatory cytokines (e.g. interleukin-1, interleukin-6, interleukin-8) and promotes recruitment of cells to the airway. In an experimental RV infection study of healthy subjects, peripheral blood neutrophilia and increased IL-8 levels have been noted within a day of inoculation followed a few days later with increase in airway neutrophils. (Jarjour et al. 2000). Following experimental RV infection of healthy subjects and mild asthmatics, Fraenkel and colleagues reported an association between bronchial hyperresponsivenes and recruitment of lymphocytes and eosinophils recruitment to the airway (Fraenkel et al. 1995). Experimental RV infection of healthy non-atopc individuals is also associated with increased expression of 5-lipoxygenase (5-LO) pathways (Seymour et al. 2002) and increased airways levels of leukotrienes and prostanoids both of which are known to enhance cough response to tussive stimuli (Niimi 2013; Stone et al. 1992).

The evidence to date therefore would tend to suggest that viral infection upregulates the cough reflex indirectly via the sensitising effects of inflammatory cells and cytokines induced by the infecting virus. However, a direct effect of respiratory virus on airway nerves needs to be considered as sensory nerves themselves are known to express the virus receptor ICAM-1 (Nie et al. 2012) and Toll-like receptors (TLRs) which play a key role in host defence during microbial infection (Lafon et al. 2006). Elucidating precisely how viruses may exert a direct effect requires a more detailed study of human airway sensory nerves. In a recent study, which used a neuronally differentiated human neuroblastoma cell line as a model of sensory neurons, infection with human rhinovirus 16 serotype caused upregulation of expression of TRP channels by distinct and channel-specific mechanisms (Abdullah et al. 2014). The increase in TRPA1 and TRPV1 levels was mediated by inflammatory cytokines including nerve growth factor (NGF) whereas TRPM8 required replicating virus. However immortalised cell lines are not likely to accurately represent the human *in vivo* situation and studies on human sensory nerves are hampered by difficulty accessing human tissue with both nerve endings and neuronal cell bodies present. A variety of intact and isolated animal preparations (described below) have helped in this regard and recently a novel technique to develop an adult human stem-cell sensory neuronal model has been described (Clarke et al. 2014). These approaches are providing important mechanistic insight into how viruses likely perturb normal sensory neuronal function.

3. Virus Infection and Primary Sensory Nerves

The persistent itchy urge-to-cough is an obvious reminder that the function of the airway sensory nerves have been corrupted by the viral infection. Sensory nerves can be modulated in basically three ways. First, they can be acutely affected in such a manner that action potentials are discharged. Secondarily they can be rendered electrically hyperexcitable such that the threshold for an activating stimulus is decreased and the stimulus-induced action potential discharge frequency is enhanced. These effects are likely associated with various inflammatory responses and terminate once the inflammation subsides. Thirdly, the nerves

can be modulated in a more persistent fashion by changing the expression of relevant genes, i.e. neuroplasticity. In this case, the modulation can outlive the virus infection, just as some important negative consequences of viral infections such as asthma exacerbations and development of a chronic unproductive cough can outlive the actual acute viral inflammation.

3.1. Sensory nerve activation

Slow conducting afferent nerves, referred to as C-fibers, arising from vagal and spinal sensory ganglia innervate all branches of the respiratory tract. These nerves are nociceptive in that they can be activated by noxious stimuli, and by mediators of inflammation. Viral infection leads to inflammatory responses and the production of pro-inflammatory cytokines, chemokines, eicosanoids and products of oxidative stress(Chiaretti et al., 2013; Radi et al., 2010; Shiraishi et al., 2008; To et al., 2014) The sensory C-fibers express receptors for many inflammatory mediators, as well as ion channels such as TRPV1 and TRPA1 that can be stimulated by certain mediators and products of oxidative stress(Mazzone and Undem, 2009; Taylor-Clark and Undem, 2011). To activate the nerve terminating in the respiratory tract, the mediator must interact with a receptors or ion channels on the sensory nerve membrane in a manner that leads to membrane depolarization. This membrane depolarization is referred to as a “generator potential”. If the generator potential reaches the voltage threshold for voltage-gated sodium channels, an action potential is evoked that is conducted along the nerve fiber to the central terminals in the brainstem. Invasion of the central terminals by the action potential evokes neurotransmitter release for synaptic transmission with secondary neurons.

3.2. Increase Sensory Nerve Excitability

Certain mediators can interact with receptors on the sensory nerve terminals in a manner that does not lead to a generator potential, but rather changes properties of certain ion channels rendering the nerve are more susceptible to activating stimuli. For example, prostaglandin E2 can interact with EP receptors on vagal afferent C-fibers causing the production of cAMP. The cAMP can lead to phosphorylation of certain voltage-gates sodium channels thereby increasing their sensitivity to membrane voltage. Virus infection is commonly associated with increases in COX2 expression and the production of epithelial prostanoids including PGE2 (Kwong and Lee, 2002; 2005). Of course, PGE2 is only one of many mediators known to increase sensory nerve excitability, and voltage-gated sodium channels in only one of many classes of ion channels the function of which can be modulated by activation of receptors for inflammatory mediators. The increase in excitability is important to recognize as it likely underlies the increase in sensory sensitivity to airborne stimuli (odors, irritants, cold dry air, etc.) that can accompanies viral infections.

3.3. Changes in sensory nerve gene expression

The gene expression in nucleus of sensory neurons can be influenced by events occurring at the distant nerve terminals. Molecules capable of interacting with afferent nerve terminals in a manner that leads to changes in gene expression in the cell bodies are referred to as neurotrophic factors. Beyond acting as developmental growth factors, neurotrophic factors

are now recognized as mediators that are increased at sites of inflammation, including airway viral inflammation (Chiaretti et al., 2013).

Neurotrophic factors interact with receptors expressed on sensory nerve endings in a peripheral target tissue, and via retrograde transport mechanisms, cause changes in gene expression in nerve cell bodies situated in the distant sensory ganglion. With respect to sensory nerves two families of neurotrophic factors are particularly relevant. One family is referred to as neurotrophins and comprise nerve growth factor (NGF) brain derived neurotophic factor (BDNF), neuortrophin 3 and neurotrophin 4 (NT3 and NT4). The second family of neurotrophic factors is the GDNF family ligands (GFLs) that comprise glial derived neurotrophic factor (GDNF) neurturin, artemin, and persephin. Each of these factors can bind with high affinity and selectivity to particular neurotrophic factor receptors.

How a given sensory neuron in the airways responds to neurotrophic factors will depend on the specific receptors it expresses. In healthy animals the low threshold mechanosensitive cough nerves that terminate in the extrapulmonary airways preferentially express the receptor TrkB (receptor for BDNFand NT3) as well as GFRα1, GFRα2, and GFRα3 (receptors for GDNF, neurturin, and artemin, respectively). These neurons also express RET, the requisite signaling molecule for all GFRα receptors (Lieu et al., 2011). The C-fibers in the airways also express TrkA (NGF receptor) TRKB and GFRαs, depending on the subtype of C-fiber in question.

Studies on the guinea pig extrapulmonary Aδ cough nerves provide relevant examples of phenotypic changes that may occur with viral infection. Typically these nerves do not express TRPV1 or Substance P. As mentioned above, nerves express the receptors for BDNF and GDNF. Exposing the trachea to BDNF or GDNF causes *de novo* production of functional TRPV1 and TRPA1. This means infections that lead the production of these neuotrophic factors can lead to a qualitative change in types of stimuli capable of activating the nerves, i.e. stimulus that that may go unrecognized in healthy subjects, could be perceived as a cough-inducing irritant in an infected individual. Exposing guinea pigs to respiratory viral infection also leads to the *de novo* expression of substance P in the Aδ cough nerve (Carr et al., 2002). When neuropeptides are released from the central terminals they can have profound effects on the synaptic transmission thereby altering the interpretation by the CNS of the signals arriving from the airway. The changes in nerve phenotype may therefore change both the stimulus activation profile, as well as the neuronal consequence of a given stimulus.

4. Virus Infection and Central Processing Involved in Cough

Changes in primary afferent neurophysiology subsequent to pulmonary viral infection would be predicted to alter the synaptic integration of peripheral inputs at the level of the brainstem. Indeed, it has been widely speculated that events comparable to central sensitization, described in detail in models of sensitized pain, might manifest in the brainstem when abnormal airway afferent signals are induced (Chung et al., 2013; O'Neill et al., 2013). In sensitized pain, central sensitization occurs as a result of convergent or sustained inputs from primary afferent sources that become significantly amplified by

second order integration neurons. This typically involves a neuroinflammatory component in which the increased neural activity drives the recruitment and activation of astrocytes and microglia which in turn release mediators capable of modulating synaptic integration and/or altering gene expression within second and higher order neurons of the pain circuitry (Scholz and Woolf, 2007). The net result of this is enhanced pain to painful stimuli (hyperalgesia) or the experience of pain in response to normally subthreshold or innocuous stimuli (allodynia).

With respect to cough, simultaneous subthreshold inputs from neuropeptide expressing airway nociceptors and airway mechanosensors can significantly lower the cough reflex threshold such that normally innocuous stimuli induce coughing (allotussia) (Mazzone et al., 2005). This probably manifests due to functional convergence between airway nociceptors and mechanoreceptors onto common integration neurons in the nucleus of the solitary tract of the brainstem. Neuropeptides are important in this process as blocking the actions of substance P centrally prevents the development of allotussia (Mazzone et al 2005). In this regard, it is interesting (as described above) that pulmonary viral infections increase neuropeptide expression in airway mechanoreceptors, suggesting that this additional substance P could be available to drive central sensitization, even in the absence of airway nociceptor inputs (Carr et al., 2002). Glutamatergic transmission is also likely involved as cough afferent inputs are encoded in the brainstem when NMDA receptor activation is unmasked. Thus, normally NMDA receptors contribute little to synaptic transmission in the nucleus of the solitary tract because the channel pore is blocked by a magnesium ion at normal resting membrane potentials. High frequency inputs, which are needed to encode cough, appear to unblock NMDA channels and there is a substantive literature in the spinal cord documenting the important role of NMDA-dependent processes in central sensitization (Canning and Mori, 2011). However, whether viral infection produces the central inflammatory component characteristic of central sensitization is unknown.

Alterations in synaptic efficacy in the brainstem following pulmonary viral infection might in turn lead to changes in the amount or type of ascending inputs to the supramedullary networks known to be important for encoding cough and the associated sensation of the urge to cough. Recent studies have described in some detail the ascending higher order circuits in receipt of airway sensory inputs using neural circuit tracing in animals and functional brain imaging in humans (Farrell et al., 2012; Mazzone et al., 2007; McGovern et al., 2012; McGovern et al., 2014). In rodents, second order brainstem neurons in receipt of airway inputs are located in the caudal nucleus of the solitary tract and the medullary trigeminal complex in and around the paratrigeminal nuclei. Efferent projections arising from these integration sites terminate in pontine, thalamic, subthalamic and other sub cortical nuclei which in turn provide inputs to cortical sites including the primary and secondary sensory cortex, the insula and the cingulate cortex (McGovern et al., 2012; 2014). However, the nature of the ascending pathways arising from the nucleus of the solitary tract and paratrigeminal nucleus may not be equivalent as notable differences exist between the brainstem terminations and resultant ascending circuits in receipt of upper versus lower airway afferent inputs, the former thought to be more important for eliciting coughing (Canning et al., 2004; McGovern et al., 2014).

The existence of several distinct functional circuits is supported by studies in humans which have shown that higher brain networks are important for the complex sensory, motor and cognitive aspects of coughing. Thus, the sensory dimension of cough (often referred to as the urge-to-cough) is encoded in somatosensory regions of the brain whereas central conscious encoding of cough stimulus intensity appears to require processing in the insula cortex (Ando et al., 2014; Farrell et al., 2012). Human studies have also shown the existence of a descending inhibitory circuit that allows for voluntary/conscious suppression of cough and this requires activity in the inferior frontal gyrus, ventromedial prefrontal cortex and insula cortex, regions previously shown to be involved in generalized motor suppression (Mazzone et al., 2011; Mazzone et al., 2015).

There have been no reported studies of how these higher brain pathways behave in models of airways disease or in patients with cough. However, pulmonary viral infections are known to produce persistent (post-viral or post-infectious) cough in some patients with ongoing perception of urge-to-cough and loss of motor control of coughing. Thus, we speculate that viral infection may alter these central neural networks, whether as a driver of persistent aberrant coughing or indeed as a consequence of it. In support of this, supraspinal plasticity is known to occur in chronic pain patients and this is thought to be a contributing factor in the maintenance and/or development of chronic pain (Ho et al., 2013; Leong et al., 2011; Zambreanu et al., 2005).

5. Concluding Remarks

Although significant progress has been made towards describing the mechanisms by which respiratory viral infections perturb the function of the neural elements that control coughing, there are still many questions to be answered before novel therapeutic approaches will be available for treating patients with persistent virally-induced coughing.

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