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Review

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.
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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 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 [13,48]. 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 [24,42]. 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 [16]. 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 [22]. 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

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host with an abnormally sensitive airway which manifests clinically as troublesome bouts of cough triggered by exposure to low level physical and chemical stimuli [39]. 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 [4]. 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 [19]. 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 [25]. Other tools such as the Wisconsin Upper Respiratory Symptom Survey (WURSS) have since been developed and validated in naturally occurring colds [3]. 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 [43]. 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 [46]. 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 [12,14]. 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 [20,56,58] and is a common cause of asthma and COPD exacerbations [33]. 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 [57] which contrasts the higher prevalence of cough reported by patients with naturally occurring colds [5]. In those with clinical symptoms rhinovirus is often recovered from the lower airway [18,21]. 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 [26]. 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 [17]. Experimental RV infection of healthy non-atopc individuals is also associated with increased expression of 5-lipoxygenase (5-LO) pathways [51] and increased airways levels of leukotrienes and prostanoids both of which are known to enhance cough response to tussive stimuli [45,53].

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 [44] and Toll-like receptors (TLRs) which play a key role in host defence during microbial infection [29]. 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 [1]. 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 [11]. 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

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