UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

What About Cough?

Stanley I. Rubin, DVM, MS
Diplomate ACVIM
Clinical Professor
Department of Veterinary Clinical Medicine

www.uiuc.edu

Disclosures

- Consulting, AVL Laboratories, St. Louis, MO

Outline

- Introduction
- Roles of Cough
- Pathologic impact of cough
- Phases of cough
- Animal models of cough
- Physiology of cough
- Treatment of cough

Introduction

- Common clinical problem in both small animal practice/human medicine
- Frequently the presenting complaint in vet med
- Most common complaint for human patients
- Prevalence rates for chronic cough in people 10 – 12%
- $6.8 billion dollars for over the counter remedies

Introduction

- Much of our understanding comes from experimental studies in animals
- Little translation of research to aid mgmt of cough in pets
- Clinician should always undertake diagnostic workup to make a definitive diagnosis
- Thoracic radiology, ultrasonography, echocardiography, CT, MRI, bronchoscopy, TTW/BAL, parasitology, serology, urine Ag tests, PCR, CBC, serum biochemistry, urine analysis

Introduction

- Treatment of underlying disorder is usually the most efficient way to manage
- Sometimes there are conditions for which there is no specific treatment and symptomatic management may improve the quality of life for the pet and owner

Pathophysiological Roles of Cough

- **Beneficial:**
  - Preserves gas-exchanging functions of lung by clearing secretions and debris from airways
  - Protects respiratory tract from inhaled irritants and foreign materials
  - Consequences of impaired cough reflex
    - Aspiration pneumonia

Pathophysiological Roles of Cough

- **Pathological impact of cough:**
  - Mechanism for spread of respiratory infections, eg. Influenza
  - Cough detracts from quality of patient's and owner's lives
  - May interfere with normal daily activities and sleep
  - May lead to euthanasia

Phases of Cough

- **Cough reflex - 3 phases:**
  - Inspiratory phase: enhanced contraction of diaphragm and abductor muscles of larynx
  - Expiratory/compressive phase: forced expiratory effort against transiently closed glottis
  - Expulsive phase: Sudden glottal opening and forceful contraction of the expiratory muscles with rapid expulsion of air
  - Serves to clear mucus/debris from airways

Phases of Cough

- Expiratory reflex (ER)
  - Induced by mechanical/chemical stimulation of vocal folds or upper tracheal segments
  - Characterized by:
    - Glottal closure and forced expiration
    - Followed by glottal opening and rapid expulsion of air
  - Prevents aspiration

Phases of Cough

- Cough often comprises combination of two motor acts:
  - True cough
  - Expiratory reflex (ER)
- Cough bout, epoch, attack
  - May consist of cough followed by expiratory efforts;
  - Or when the larynx is stimulated, the response may be an ER followed by true cough

Control of Cough

- A visceral reflex with both voluntary and involuntary control
- Number & force of coughs under conscious control in people
- Makes assessment of antitussive medications & other therapies difficult
- Conscious control in animals?

Animal Models

- Much of understanding of physiology of cough comes from lab experiments using dogs, cats, rabbits, guinea pigs, monkeys, rates and mice
- Mice and rats do not cough in a manner similar to most mammals
- Many studies under deep, surgical anesthesia involving terminal experiments
- Decerebrate, paralyzed, artificially ventilated cats during fictive cough induced by laryngeal nerve stimulation

Animal Models

- Sophisticated studies to perform neuronal mapping and localize brainstem and higher centers
  - Immunohistochemistry
- *In vitro* models that utilize isolated vagus/upper airway preparations from guinea pigs
  - Action potentials are recorded from cell bodies after tussive stimuli are applied to a specific receptor field to study mechanical/chemical sensitivities or changes in excitability
- No animal models exist where animals cough spontaneously as occurs in human disease

Physiology of Cough

- Reflex arc
  - Afferent receptors and pathway
  - Central integration
  - Efferent pathways/respiratory muscles

Cough Receptors

- Two kinds
  - C-fibers; aka c-fiber nociceptors
  - Cough receptors
- Pulmonary stretch receptors
  - No evidence that initiate coughing
  - Regulate tidal volumes and respiratory rate
  - May modulate the magnitude and duration of inspiratory and expiratory phases of coughing

C-fibers

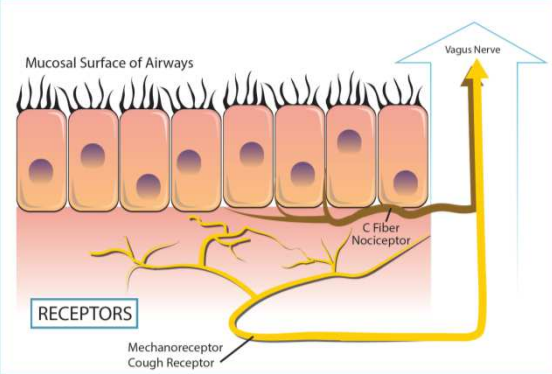
- Terminations present around mucosal surfaces and airways; primarily in the larynx, trachea, carina and large intrapulmonary bronchi
- Sensitive to variety of inhaled or locally produced mediators
- Also characterized by sensitivity to bradykinin and ion channel activators (TRPV1, TRPA1)

C-fibers

- Also characterized by sensitivity to bradykinin and ion channel activators
  - TRPV1: capsaicin, protons
    - Antagonists:
  - TRPA1: ozone, allyl isothiocyanate
    - Antagonists: Na+ channel blockers, opioids
- Other activators: substance P, PGE_2, adenosine, serotonin, nicotine
- End action blocked by anesthesia

Cough Receptors

- Innervating extrapulmonary airways in trachea, main stem and segmental bronchi
- Also referred to as Aδ
- Myelinated, mechanically sensitive
- Activated by protons, capsaicin insensitive
- Do not express ion channels TRPA1, TRPV1
- Contains α_3-containing isozyme of Na^+/K^+ATPase



Afferent Nerves - Other

- Other afferent nerves to the CNS are thought to play a role in cough control
- Ear
- Nasal & upper airways
- Pharynx
- Esophagus

GERD & Cough

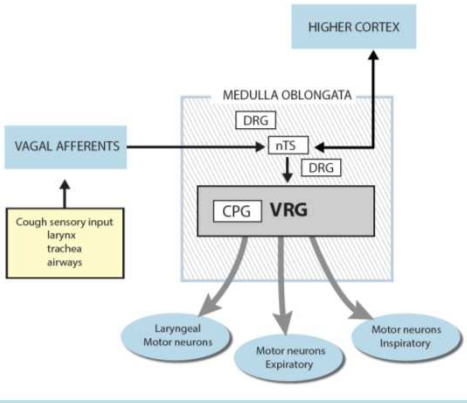
- Clear association between chronic cough & gastroesophageal reflux disease in people
- Treatment of reflux dz reduces coughing in subset of people
- Locally or centrally mediated airway reflexes can be initiated from stomach or esophagus
- Neuronal projections between esophageal and airway autonomic ganglia that can increase mucus secretion or bronchoconstriction, which further promotes coughing
- Convergence of central esophageal and airway afferent pathways within the brain

Afferent Pathways

- Afferent pathways are via the bronchopulmonary vagal afferent nerves
- Cell bodies of c-fibers and cough receptors located in jugular and nodose vagal ganglia
- Vagal afferent neurons from airway receptors project to the brainstem

Central Integration

- Historically cough thought to originate from distinct neural center in brain
- Same respiratory neurons that produce the normal respiratory rhythm are involved in producing the motor patterns for protective reflexes such as ER, cough, sneeze
- The central pattern generator (CPG) within the respiratory center controls the timing and magnitude of coughing
- Located in the brainstem



Efferent Pathways

- Efferent pathways of cough convey command to the respiratory muscles via phrenic, intercostal and lumbar nerves
- Some commands via cranial nerves to laryngeal intrinsic muscles
- Sympathetic and parasympathetic nerves supplying the airway smooth muscle and glands

Motor Pattern of Cough

- Coordinated action of several muscles in upper airways and chest walls
- Upper airway muscles in mouth and larynx influence airflow
- Inspiratory muscles; diaphragm external intercostals
- Expiratory muscles of abdominal wall are activated during compressive and expulsive phases of cough and ER

Management of Cough

- Clinician should always undertake diagnostic workup to make a definitive diagnosis
- Thoracic radiology, ultrasonography, echocardiography, CT, MRI, bronchoscopy, TTW/BAL, parasitology, serology, urine Ag tests, PCR, CBC, serum biochemistry, urine analysis

Management of Cough

- Antitussives for symptomatic management of cough
  - Kennel cough and other acute URI
  - Tracheal collapse
  - Chronic bronchitis
  - Tracheal compression dt LA enlargement

Opiates

- Centrally acting
- Codeine, hydrocodone, morphine, butorphanol, diphenoxylate
- Though to be gold standard
- Antitussive efficacy in people unpredictable and inconsistent

Hydrocodone

- Hydrocodone (Hycodan®, Hydromet®, generic)
- Usually combined with homatropine
- 5 mg tab contains 1.5 mg homatropine
- 1 mg hydrocodone/ 0.3 mg homatropine per ml of elixir
- Dose 0.5 – 1.5 mg/kg q 8h PO
- Cost: 5 mg tab x60 = $30, 240 ml elixir = $30
- DEA, Schedule II

Butorphanol

- May have shorter duration of antitussive effect
- Available in 1, 5, & 10 mg tablets and injectable
- Antitussive dose 0.5 – 1.0 mg/kg q 6-12h PO
- DEA, Schedule IV

Diphenoxylate

- Aka Lomotil®
- Usually used as antidiarrheal
- 2.5 mg tabs, contains atropine
- Dose 0.25 – 0.5 mg/kg q 12 h PO
- May cause constipation
- Cost 2.5 mg tab x 120 = $40-50

Dextromethorphan

- Centrally acting
- Similar chemical structure to opiates, but does not bind to opiate receptors
- Pharmacology not completely understood; NMDA antagonist
- Questionable clinical efficacy
- Included in many OTC preparations
- Not recommended as antitussive

Trazadone

- Antianxiety agent with nonspecific sedating properties
- Centrally acting; serotonin 2A receptor antagonist and weak SSRI
- Used in dogs for events that trigger anxiety, eg. Thunderstorms
- May help to diminish “triggers” that cause cough in dogs
- Available in 50, 100, 150 & 300 mg tabs
- Dose 5 mg/kg q8-24 h PO

Maropitant

- Aka Cerenia®
- NK-1 receptor antagonist
- Substance P has been implicated in both central and peripheral sensitization of cough reflex
- 2 mg/kg q 48h x 14 d in dogs with chronic bronchitis decreased cough frequency

Grobman M, Reinero. J. Vet. Intern Med 2016;30:847-852

Guaifenesin

- In numerous OTC preparations
- Expectorant
- Believed to alleviate cough discomfort by increasing sputum volume and decreasing viscosity
- May have an antitussive action in acute viral cough in people

Other Drugs

- Proton pump inhibitors
- Amitriptyline
- Gabapentin

Questions?

- References available on request