COMMENTARY

Chemically Induced Mice Cough Model

Riffat Farooqui

ABSTRACT:
Cough is the most common respiratory symptom that has been experienced by every human. Both the chemically and mechanically sensitive airway nerves take part in mediating the cough reflex and establishing synapses in the brainstem's caudal two-thirds of the nucleus tractus solitaries. The sensation of an "urge to cough" is ostensibly associated with activation of broncho- pulmonary C-fibers. These C-fiber nerves become directly activated, 'sensitized' or 'hyper-activated' by chemicals such as capsaicin, bradykinin, adenosine, prostaglandin type E-2 (PGE2), citric acid, hypertonic saline solution, Sulfur dioxide (SO2). Chemically induced cough facilitates the quantification of cough and the assessment of antitussive effects of specific therapeutic agents. Sulphur dioxide gas has been used to elicit cough in various experimental animals like cats, rats and mice.
Key Words: Cough, Cough model, Mice, Tussive, Sulfur dioxide gas.

INTRODUCTION:

Cough can be defined as a forced expulsive maneuver usually against a closed glottis and is associated with a characteristic sound.[1] It can be measured subjectively using symptom scores and specific quality-of-life measures, and objectively by measuring cough numbers and intensity, and by assessing the cough response to capsaicin, citric acid and other chemicals.[2] Cough often presents as the first and most persistent symptom of many respiratory diseases and some non-respiratory disorders, but can also be idiopathic, and is a common respiratory complaint for which medical attention is sought.[3] In the modern world of science animal models specially the laboratory animal models play a vital role in the drug discovery process. They are also employed for testing various new properties and effects of existing and old drugs. Enhanced coughing can be produced in a variety of animal models, including guinea pig, cat, dog and pig etc. Typically, airway inflammation has been produced by sensitization, exposure to cigarette smoke, sulphur dioxide or angiotensin-converting enzyme inhibitors in different animal models.[4]

Cough can be induced in experimental animals by the following[5]

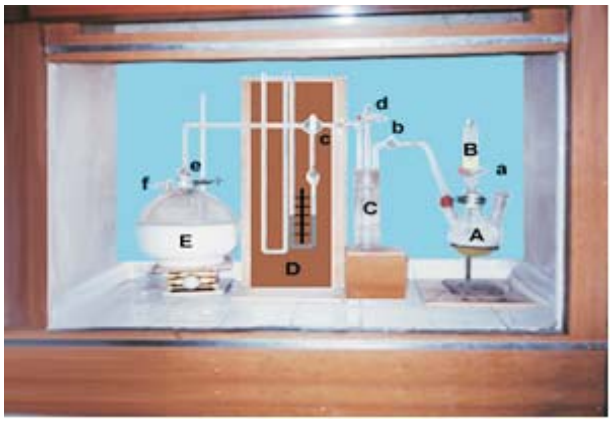
- Chemical stimulation of sensory nerve
- Mechanical stimulation of sensory nerve
- Electrical stimulation of sensory nerve

The chemical induced cough facilitates the quantification of cough and the assessment of antitussive effects of specific therapy.[6] Sulphur dioxide gas has been used to elicit cough in various experimental animals, e.g., in cats[7] , in rats[8], in mice[9] etc. In animal models, there is activation of interneuron pathways located between the medullary nucleus tractus solitarius and the nucleus ambiguus during coughing. Stimulation of the superior laryngeal nerve can evoke different laryngeal adductor muscle responses including coughing, swallowing, gagging, laryngeal spasms, bronchoconstriction, apnea, and retching. The type of the evoked reflex response depends on the considerations of the stimulus used, [10, 11] and is utilized in conducting various types of research projects.

In 2007 the author employed mice cough model developed by Miyagoshi & colleagues (1986) to test activity of an antitussive drug.[9]

Cough Model Developed By Miyagoshi & Colleagues: Apparatus and Solutions: A is 500 ml three-necked flask containing aqueous saturated sodium hydrogen sulfite solution. By opening the cock of a dropping funnel B, conc. sulfuric acid is introduced to generate sulfur dioxide gas. Sulfur dioxide gas is filled previously in A and C, a gas reservoir, and by opening cocks c and b, pressure in the gas C is elevated which is recorded by water manometer D. Then the cock b is closed and the cock d is opened slightly until the pressure in D (11 mm I.D.) reaches to 75 mm H2O, when the cock d is closed (Figure 1).

Figure 1
Apparatus used for antitussive activity



A: Three-necked round bottom flask, containing 39% NaHSO3 solution, B: dropping funnel having conc. H2SO4, C: Gas reservoir, D: water manometer, E: Desiccator.

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Method/ Technique:

Testing material was orally administered to mice. Initially the cough responses were observed at zero (0) minute by placing the animals in the desiccator E. The cock C, F and E were opened in order, and when the pressure in D became zero mm H2O, the cock E and F were closed immediately. A certain amount of sulfur dioxide was introduced in the desiccator E by these operations. After one minute of introducing sulfur dioxide gas, the mice were taken out of the desiccator and frequency of cough was observed for 5 minutes in an up-ended filter funnel with a stethoscope at the tip, in which the mouse was confined. In the same fashion the frequency of cough was observed at 30 and 60 minutes respectively. The effects of long-term exposure to sulfur dioxide can be studied only in experimental animals. At concentrations in excess of 28.6 mg/m3 (10 ppm), prolonged exposure has been shown to produce damage to the epithelium of the airways. This may be followed by epithelial hyperplasia, a dose-related increase in goblet cells and hypertrophy of the submucosal glands. These changes are similar to those seen in chronic bronchitis in humans. Prolonged exposure of rats to sulfur dioxide has also been used to produce a chronic cough model for testing antitussive agents.[12]

Search words of cough, cough model, mice, tussive and sulfur dioxide gas from 1986 to 2014 using google search engine revealed use of 5 chemicals with 5 different methods for inducing cough in animal models (Table.1)[13,14,15,16,17,18.]

Table 1

S.N	Chemical	Animal Used	Author	Year of Study
1	Adenosine and Capsaicin	Mice	Ryan P. Vaughan	2006
2	Citric acid and Capsaicin	Guinea pig	Sum Yee Leung	2007
3	Sulphur dioxide (SO2)	Mice	Gupta YK	2009
4	Acrolein, Acetic acid & Cyclohexanone	Mice	Daniel N. Willis	2011
5	Sulphur dioxide (SO2)	Mice	Rizwan ul Haq	2013
6	Sulphur dioxide (SO2)	Mice	Riffat Farooqui	2014

Most of these studies have utilized mice to make cough model. It is evident that sulphur dioxide (SO_2) was used alone by three researchers (including author) in 2009, 2013 and 2014 respectively for the investigation of antitussive materials whereas other chemicals were used by researchers in combinations. It is said that mice demonstrate an increased cough response to sulphur dioxide gas, this explains development of exacerbated cough following sulphur dioxide gas exposure in this laboratory animal. Mice cough model is thus a convenient method for research studies and estimation of antitussive effects of agents.

Sulphur dioxide gas induced murine cough model, developed by Miyagoshi and colleagues in 1986 is a simple, reliable and reproducible method that can be used to investigate antitussive efficacy of testing material. Enhancing the literature search in terms of time frame, number of search engines and comparing various available methods for inducing cough model to determine the most simple, reliable and reproducible method, are open avenues for future research.

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