Influence of central antitussive drugs on the cough motor pattern

DONALD C. BOLSER, 1 J O H N A. HEY, 2 AND RICHARD W. CHAPMAN 2

1 Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, Florida 32606; and 2 Allergy, Schering-Plough Research Institute, Kenilworth, New Jersey 07033

Bolser, Donald C., John A. Hey, and Richard W. Chapman. Influence of central antitussive drugs on the cough motor pattern. J. Appl. Physiol. 86(3): 1017–1024, 1999.—The present study was conducted to determine the effects of administration of centrally active antitussive drugs on the cough motor pattern. Electromyograms of diaphragm and rectus abdominis muscles were recorded in anesthetized, spontaneously breathing cats. Cough was produced by mechanical stimulation of the intrathoracic trachea. Centrally acting drugs administered included codeine, morphine, dextromethorphan, baclofen, CP-99,994, and SR-48,968. Intravertebral artery administration of all drugs reduced cough number (number of coughs per stimulus trial) and rectus abdominis burst amplitude in a dose-dependent manner. Codeine, dextromethorphan, CP-99,994, SR-48,968, and baclofen had no effect on cough cycle timing (CT tot) or diaphragm amplitude during cough, even at doses that inhibited cough number by 80–90%. Morphine lengthened CT tot and inhibited diaphragm amplitude during cough, but these effects were not dose dependent. Only CP-99,994 altered the eupneic respiratory pattern. Central antitussive drugs primarily suppress cough by inhibition of expiratory motor drive and cough number. CT tot and inspiratory motor drive are relatively insensitive to the effects of these drugs. CT tot can be controlled independently from cough number.

diaphragm; abdominal; rectus abdominis; brain stem; control of breathing

ANTITUSSIVE DRUGS, such as codeine and dextromethorphan, are among the most commonly used prescription and over-the-counter drugs in the world (12). These drugs are broadly classified into two groups based on their site of action: peripheral or central. Peripheral antitussive drugs act outside the central nervous system (CNS) to inhibit cough by suppressing the responsiveness of one or more vagal sensory receptors that produce cough (1, 2, 4, 22). Central antitussive drugs act within the CNS at the level of the brain stem, where the basic neural circuitry responsible for cough is located (23, 27–29). However, our understanding of the exact mechanisms and sites of action that centrally active antitussive drugs act within this system is incomplete.

Cough is a multiphasic motor task which consists of sequential large increases in motor drive to inspiratory and expiratory muscles. This cough motor pattern has both spatial and temporal characteristics. The spatial characteristics of cough include the magnitude of motor drive to different muscles. The temporal characteristics of cough consist of the duration of each cough (the cough cycle) and its component phases (inspiration, compression, expulsion).

Shannon and co-workers (27–29) have recently proposed a model of the central neural circuitry responsible for the cough motor pattern. A basic feature of this model is that the eupneic respiratory pattern and the cough motor pattern are produced by essentially the same neural components. Although this pattern generator normally controls breathing, its behavior is modified to produce cough by excitatory inputs from medullary second-order interneurons mediating pulmonary rapidly and slowly adapting receptor (RAR and SAR, respectively)—afferent information (27–29). Centrally active antitussive drugs could act at any level within this system. For example, these drugs could suppress the responsiveness of components of the central pathway for transmitting vagal sensory information (second-order interneurons) and/or have more complex effects on the motor pattern generator for cough (6, 8, 11). A fundamental approach to this problem is to evaluate the effects of antitussive drugs on specific components of the cough motor pattern. In particular, cycle timing is a direct index of the function of central pattern generators, and perturbations that alter cycle timing do so by directly affecting components of these generators. Although many studies have addressed various aspects of the action of commonly used antitussive drugs, a complete analysis of the effects of these drugs on the cough motor pattern has never been reported.

Specifically, there is no information on the effects of these drugs on cough-cycle timing (CT tot). This information is essential if we are to more fully understand the organization of the central pattern generator for cough as well as how its function is modified by antitussive drugs.

We addressed this problem in two ways. First, we used a model of mechanically induced cough in the cat (8), in which centrally acting antitussive drugs are much more potent to inhibit cough (20-fold or greater) when administered by the vertebral artery than by the intravenous route (7, 8, 11). Because of the large difference in potencies, known centrally acting antitussive drugs can be administered by the vertebral artery route in dosage ranges that preclude any possibility of peripheral effects. Second, we compared the effects of central antitussive drugs on several components of cough. These components included cough number (the number of coughs in response to a stimulus), the magnitude of motor drive to inspiratory and expiratory
muscules during this defensive reflex, and the duration of each cough (CT_{tot}). Our previous work showed that codeine has differential effects on some of these components in a model of fictive cough (6). On the basis of preliminary observations in other experiments, we speculated that centrally active antitussive drugs would inhibit these components of cough in patterns characteristic of their functional site and mechanism of action. Specifically, we expected that central administration of antitussive drugs would result in suppression of cough number and expiratory muscle electromyogram (EMG) burst amplitude but would have no effect on cough-phase timing or amplitude of diaphragm EMG bursts.

METHODS

Cats of either sex (n = 30, 2.5–4.5 kg) were anesthetized with pentobarbital sodium (35 mg/kg ip). End-tidal CO$_2$ (ET$_{CO_2}$) was monitored, and supplemental anesthetic (5 mg/kg iv) was administered when this value dropped to <3.9%. Animals with ET$_{CO_2}$ >5.0% usually did not cough consistently and were excluded from analysis. Supplemental anesthetic was administered as necessary (5 mg/kg iv). Atropine sulfate (1 mg/kg iv) was administered to block reflex airway secretions. Body temperature was maintained at 37 ± 1°C with an electric heating pad. The trachea was cannulated to allow access to the intrathoracic airway. The femoral artery and vein were cannulated in all animals to arterial blood pressure and to administer supplemental anesthetic, respectively. The left axillary artery was cannulated, and the cannula was ligated. Evas blue dye was injected into the catheter at the end of the experiment, and proper placement of the catheter was confirmed postmortem. Animals with dye labeling of the muscles of the chest wall or intrathoracic tissues were rejected. The animals were placed in a supine position.

EMGs from the diaphragm and rectus abdominis muscles were recorded with the use of bipolar tungsten-wire electrodes. The diaphragm electrodes were placed through a small midline abdominal incision, which was subsequently closed. The diaphragm electrodes were placed through a small midline abdominal incision, which was subsequently closed. The EMGs were amplified, filtered (0.5–10 kHz), and integrated with a resistance-capacitance circuit (100-ms time constant). The integrated EMGs were displayed on a chart recorder and recorded on videotape.

Cough is characterized by coordinated bursts of activity in inspiratory and expiratory muscles (23). Cough was defined as a large burst of EMG activity in the diaphragm that is immediately followed by a burst of EMG activity in the rectus abdominis muscle (5, 7, 8). This definition differentiates augmented breaths, the aspiration reflex, or the expiration reflex from cough (30–33). Coughing was produced by mechanical stimulation of the intrathoracic trachea with a thin flexible polyethylene cannula for 10 s per stimulus trial. During each trial, the cannula was repetitively moved in the trachea at a frequency of ~2 Hz.

The antitussive activity of selected antitussive drugs was evaluated from cumulative dose responses obtained after intravertebral artery (ia) administration of each compound. Each animal received only one compound. The protocol consisted of application of five consecutive mechanical stimulus trials after vehicle administration. One minute elapsed between stimulus trials. Stimulus trials were applied at 1-min intervals after each dose of compound, for a total of five stimulus trials between doses. Approximately 7 min elapsed between each dose of compound. Each animal received only one drug.

Components of the cough response that were measured included cough number (number of coughs per stimulus trial), cough inspiratory amplitude (integrated diaphragm EMG burst amplitude during cough), cough expiratory amplitude (integrated rectus abdominis EMG burst amplitude during cough), CT$_{tot}$, eupneic respiratory cycle time (T$_{tot}$), and eupneic diaphragm amplitude (integrated diaphragm amplitude during spontaneous breathing). Measurements of cough cycle duration and of burst amplitudes of integrated diaphragm and rectus abdominis EMGs during cough are illustrated in Fig. 1; these measurements were assessed by visual inspection of the chart record. Amplitudes of these EMGs during cough were expressed as a percentage of the largest burst observed in each animal. The cough response after each dose of compound was determined by averaging cough number, CT$_{tot}$ (in s), normalized cough inspiratory and cough expiratory amplitudes observed during the five stimulus trials. These values were then expressed as percentages of the same measurements taken during the control period.

After each dose of drug, T$_{tot}$ and eupneic diaphragm burst amplitude (in arbitrary units) were measured. These values were derived from the integrated diaphragm EMG by visual inspection of the chart record and were expressed as a percentage of the same measurements taken during the control period.

Statistics. Data are expressed as means ± SE. One-way analysis of variance was used to evaluate differences between mean values and slopes of dose responses. Post hoc analysis of the data for analysis of variance was conducted by the Newman-Keuls method. P < 0.05 was considered significant.

Compounds. Centrally acting drugs used in this study included codeine (opioid receptor agonist), morphine (a µ-opioid receptor agonist), dextromethorphan (a ν-receptor agonist and N-methyl-D-aspartate channel modulator), [(+)N-methyl-(4-(4-acetylamino-4-phenyl piperidino)-2-(3, 4-dichlorophenyl)butyl]benzamide (SR-48,968; a tachykinin NK$_{1}$-receptor antagonist), (+)(2R,3R)-3-(2-methoxybenzylamino)-2-phenylpiperidine (CP-99,994; a tachykinin NK$_{1}$-receptor antagonist), and baclofen [a γ-amino-n-butyric acid (GABA$_{A}$)-receptor agonist]. The doses of these drugs administered were (in mg/kg) 0.001–0.1 codeine, 0.001–0.01 morphine, 0.001–0.03 dextromethorphan, 0.001–0.1 SR-48,968, 0.0001–0.01 CP-99,994, and 0.001–0.03 baclofen. Sources of the compounds used in this study were as follows: codeine and morphine (Mallinkrodt, St. Louis, MO), baclofen (Research Biochemicals, Natick, MA), and atropine sulfate and dextromethorphan (Sigma Chemical Co., St. Louis, MO). CP-99,994 and SR-48,968 were synthesized at Schering-Plough Research Institute (Kenilworth, N J). All drugs were dissolved in physiological saline. Doses were calculated as their free base.

RESULTS

The cough response to mechanical stimulation of the intrathoracic airway consisted of repetitive and large phasic increases in diaphragm and rectus abdominis EMGs (Fig. 1). Control cough number in these animals averaged 8 ± 1 coughs per stimulus. Increases in diaphragm EMG during cough before administration of drugs were 350 ± 70% greater than baseline activity.
during eupnea. There was little or no baseline activity in the rectus abdominis muscle in these animals (Fig. 1), so bursting activity in this muscle during cough could not be compared with resting activity. However, in other studies, rectus abdominis EMG amplitudes during cough exceeded EMG amplitudes during end-expiratory loads of 15 cmH2O by 250–500% (10). In the control period, CTtot (1.7 ± 1.4 s) during coughing was significantly less than Ttot during eupnea (2.6 ± 0.4 s, P < 0.01).

An example of the effect of intra-arterial codeine on the cough motor pattern is shown in Fig. 2. In the control period, 12 large diaphragm and rectus abdominis bursts were elicited during cough. After administration of a cumulative dose of codeine (0.01 mg/kg ia), only nine bursts were elicited, and the average amplitude of the rectus abdominis bursts, but not the diaphragm bursts, was reduced. After a cumulative dose of codeine (0.03 mg/kg ia), only five coughs were elicited, and the average rectus abdominis EMG was profoundly reduced compared with control. The amplitudes of the diaphragm bursts were relatively unchanged (Figs. 2 and 3). Furthermore, the reduction in the number of coughs during administration of codeine was not due to an increase in the duration of each cough cycle, as there was no change in CTtot (Fig. 2).

After administration of these drugs, phasic increases in diaphragm EMG often were observed in response to the mechanical stimulus but with no subsequent rectus abdominis burst. Examples of increases in diaphragm activity with no rectus abdominis activity in the subsequent expiratory period are shown in Fig. 1 (0.01 mg/kg codeine, first diaphragm burst; and 0.03 mg/kg codeine, first four diaphragm bursts).

The dose responses for the effects of intravertebral artery codeine, dextromethorphan, CP-99,994, SR-48,968, baclofen, and morphine on cough number, diaphragm EMG amplitude, rectus abdominis EMG amplitude, and CTtot are shown in Fig. 3. Relative to vehicle, cough number was significantly inhibited by all of the drugs (codeine, P < 0.01; dextromethorphan, P < 0.03; CP-99,994, P < 0.001, SR-48,968, P < 0.05; morphine, P < 0.01, baclofen, P < 0.01). Similarly, rectus abdominis EMG amplitude was significantly inhibited by all of the drugs (codeine, P < 0.01; dextromethorphan, P < 0.01; CP-99,994, P < 0.001; SR-48,968, P < 0.05; morphine, P < 0.01; baclofen, P < 0.01). Neither CTtot nor diaphragm amplitude was significantly altered by codeine, dextromethorphan, baclofen, CP-99,994, or SR-48,968. CTtot was significantly lengthened (by 38%; P < 0.05) by morphine at a dose of 0.003 mg/kg, but no further effect was seen with an increased dose (Fig. 3). Morphone also significantly inhibited diaphragm amplitude at the highest dose, although the slope of the dose response for the effect of morphine was not significantly different from zero (Table 1).

Significant, dose-dependent decreases in cough number and rectus abdominis EMG amplitude, but not diaphragm amplitude or CTtot, were determined by analysis of the slopes of the dose responses (Table 1) and by comparing the magnitude of change in each of the four cough parameters at each dose by using ANOVA. The slopes for inhibition of cough number and
rectus abdominis EMG amplitude by each drug were significantly different from zero. By contrast, the slopes for diaphragm EMG amplitude and CT$_{tot}$ were not significantly different from zero for any drug, although the slope for CT$_{tot}$ approached statistical significance for morphine ($P < 0.06$). The slope for suppression of cough number was significantly different from that for CT$_{tot}$ for every drug except for SR-48,968 (Table 1). Furthermore, the slope for cough number was significantly different from that for diaphragm EMG amplitude for every drug except for morphine and SR-48,968 (Table 1). The slope for inhibition of rectus abdominis

Table 1. Slopes of intra-arterial dose responses for effects of central antitussive drugs on cough number, diaphragm EMG amplitude, rectus abdominis EMG amplitude, and CT$_{tot}$ in the cat

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cough No.</th>
<th>Diaphragm Amplitude</th>
<th>Rectus Abdominis Amplitude</th>
<th>CT$_{tot}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>$-35 \pm 7$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-5 \pm 8$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-31 \pm 8$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-3 \pm 4$</td>
</tr>
<tr>
<td>Morphine</td>
<td>$-37 \pm 7$ ($P &lt; 0.01$ vs. CT$_{tot}$)</td>
<td>$-17 \pm 8$ ($P &lt; 0.05$ vs. CT$_{tot}$)</td>
<td>$-36 \pm 9$ ($P &lt; 0.01$ vs. CT$_{tot}$)</td>
<td>$16 \pm 10$</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>$-33 \pm 9$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$; $P &lt; 0.01$ vs. CT$</em>{tot}$)</td>
<td>$0 \pm 8$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$; $P &lt; 0.01$ vs. CT$</em>{tot}$)</td>
<td>$-33 \pm 8$ ($P &lt; 0.05$ vs. Dia$<em>{ampl}$; $P &lt; 0.01$ vs. CT$</em>{tot}$)</td>
<td>$1 \pm 6$</td>
</tr>
<tr>
<td>SR-48,968</td>
<td>$-23 \pm 7$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-1 \pm 7$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-13 \pm 6$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$2 \pm 5$</td>
</tr>
<tr>
<td>CP-99,994</td>
<td>$-36 \pm 7$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-5 \pm 4$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$25 \pm 1$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$2 \pm 3$</td>
</tr>
<tr>
<td>Baclofen</td>
<td>$-40 \pm 10$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$16 \pm 10$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$-34 \pm 8$ ($P &lt; 0.001$ vs. Dia$<em>{ampl}$ or CT$</em>{tot}$)</td>
<td>$15 \pm 8$</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n$, 5 cats in each treatment group. Dia$_{ampl}$, diaphragm electromyogram (EMG) amplitude; CT$_{tot}$, cough cycle timing; SR-48,968, a tachykinin NK$_{2}$-receptor antagonist; CP-99,994, a tachykinin NK$_{1}$-receptor antagonist. Negative slopes indicate dose-related inhibition of the parameter, whereas positive slopes indicate dose-related increases in the parameter.
EMG amplitude was significantly different from that for diaphragm EMG amplitude for every drug except morphine and SR-48,968 (Table 1). The slopes for inhibition of rectus abdominis EMG amplitude were significantly different from those for CTtot for every drug except SR-48,968 (Table 1). Slopes for inhibition of cough number and rectus abdominis EMG amplitude were not significantly different for any drug.

For codeine, cough number was significantly inhibited compared with diaphragm EMG amplitude (P < 0.01) and CTtot (P < 0.01) at a dose of 0.1 mg/kg. At this same dose for codeine, rectus abdominis EMG amplitude was significantly inhibited compared with CTtot (P < 0.05). Morphine, at doses of 0.001, 0.003, and 0.01 mg/kg, significantly inhibited cough number (P < 0.05, <0.001, and <0.001, respectively), rectus abdominis EMG amplitude (P < 0.05, <0.001, and <0.001, respectively), and diaphragm EMG amplitude (P < 0.05, <0.001, and <0.001, respectively) relative to CTtot. Dextromethorphan significantly inhibited cough number relative to diaphragm EMG amplitude (P < 0.001) or CTtot (P < 0.001) at a dose of 0.03 mg/kg. This dose of dextromethorphan also significantly inhibited rectus abdominis EMG amplitude relative to diaphragm EMG amplitude (P < 0.01) or CTtot (P < 0.05). Baclofen significantly inhibited cough number relative to diaphragm EMG amplitude at doses of 0.01 (P < 0.05) and 0.03 mg/kg (P < 0.05). Baclofen also significantly inhibited cough number relative to CTtot (P < 0.05) and rectus abdominis EMG amplitude relative to diaphragm EMG amplitude (P < 0.05) or CTtot (P < 0.05) at a dose of 0.03 mg/kg. CP-99,994 elicited significant decreases in cough number relative to CTtot at doses of 0.0003, 0.001, 0.003, and 0.01 mg/kg (P < 0.001 for each) and significant decreases in cough number relative to diaphragm EMG amplitude at doses of 0.003 and 0.01 mg/kg (P < 0.001 for each). CP-99,994 elicited significant decreases in rectus abdominis EMG amplitude relative to CTtot and diaphragm EMG amplitude at doses of 0.001, 0.003, and 0.01 mg/kg (P < 0.001 for each). Although no significant effects on the dose-response slopes were observed for SR-48,968, the values for inhibition of cough number by SR-48,968 were significantly different from those for diaphragm EMG amplitude and CTtot at doses of 0.01 (P < 0.05), 0.03 (P < 0.01), and 0.1 mg/kg (P < 0.01). Similarly, rectus abdominis EMG amplitude was significantly inhibited by SR-48,968 compared with diaphragm EMG amplitude or CTtot at a dose of 0.1 mg/kg (P < 0.05).

The influence of these drugs on the respiratory pattern (Ttot and diaphragm EMG amplitude during eupnea) was assessed. Except for CP-99,994, none of these drugs had any effect on Ttot during spontaneous breathing, even at doses that had profound antitussive activity (Fig. 4A). CP-99,994 produced a significant and dose-dependent decrease in Ttot (Fig. 4A), primarily by decreasing inspiratory time. None of these drugs had any significant effect on the amplitude of the diaphragm EMG during spontaneous breathing (Fig. 4B).

**DISCUSSION**

The major findings of this study are that most centrally active antitussive drugs inhibit cough number and abdominal motor activity, but not diaphragm motor activity or cycle timing, during cough. Furthermore, of the six drugs studied, only CP-99,994 significantly altered any parameter of the eupneic breathing pattern, even at doses that profoundly inhibited cough number.

This is the first report to investigate the central actions of antitussive drugs on the cough motor pattern. This also is the first report to investigate the effects of central antitussive drugs on the timing of the cough cycle. Two previous studies (6, 23) investigated the effects of intravenous administration of codeine on the cough motor pattern and had similar observations.
on the effects of this drug on cough number and the amplitudes of inspiratory and expiratory motor activity. However, the results of these previous studies could have been influenced by peripheral actions of codeine (1, 2, 21). The present study administered this drug by the intra-arterial route at doses that were too low to have significant peripheral effects (7, 8). Furthermore, all the other drugs that we used (morphine, baclofen, dextromethorphan, CP-99,994, and SR-48,968) were administered in dosage ranges that are inactive when given intravenously in this model (7–9). Indeed, several of the drugs that we investigated (baclofen, CP-99,994, and SR-48,968) appear to have no peripheral component to their action after systemic administration in this and other models (7, 9). Therefore, our findings are limited to central actions of these antitussive drugs.

Results from the present study indicate that most central antitussive drugs act by inhibition of specific components of the cough motor pattern and do not generally suppress all aspects of this motor task. In particular, these drugs suppress the number of coughs produced in response to a stimulus, but the mechanism by which this suppression of cough number occurs does not involve CTtot. This means that there is a central cough-pattern generator (27–29) and a gating mechanism that, when stimulated, permits the cough-pattern generator to produce its output. The effect of the central antitussive drugs administered in the present study was to regulate the “permissive” action of the cough-pattern-generator gating mechanism. That is, when a cough is elicited, the CTtot is based on a central pattern unaffected by these drugs. Furthermore, with the exception of the central depressant drug morphine, central antitussive drugs suppress the amplitude of expiratory motor drive, but not inspiratory motor drive, during cough. Morphine inhibited diaphragm amplitude during cough as well as cough number and expiratory burst amplitude. This finding indicates that, although it is possible to pharmacologically suppress diaphragm burst amplitude during cough, it is rare for a drug to act in this manner. Unlike the effect of morphine on cough number, this drug did not prolong CTtot in a dose-dependent manner, as indicated by a slope for the CTtot relationship that was not significantly different from zero. Furthermore, the effects of morphine on cough number cannot completely be explained by prolongation of CTtot, because the maximum effect of morphine on cough number was a reduction of ~80%, compared with a prolongation of CTtot of ~35%. Therefore our results for morphine are also consistent with separate regulation of CTtot (cough-pattern generator) and cough number (gating).

These observations have important implications for the functional organization of the central cough-pattern generator and the central site(s) of action of antitussive drugs. First, of the four components of cough (cough number, CTtot, inspiratory burst amplitude, and expiratory burst amplitude), only central mechanisms responsible for cough number and expiratory motor drive are suppressed by antitussive drugs. Central pathways responsible for CTtot and inspiratory motor drive during cough are relatively unaffected by antitussive drugs. Second, central mechanisms responsible for CTtot are independent of mechanisms responsible for cough number. The duration of the cough cycle was unchanged, even at doses of antitussive drugs that profoundly inhibited cough number. These results mean that there is a fixed central motor pattern for individual coughs and that antitussive drugs act on the motor-pattern-induction system (or gate, see below).

Shannon and co-workers (27–29) have proposed a model for the central-pattern-generation system for cough. We have condensed their model into a simplified version to illustrate aspects that our present results indicate are sensitive to the effects of antitussive drugs. The modified model (Fig. 5) is different from the parent model in several ways. First, a gating mechanism is interposed between the SAR and RAR second-order interneurons and the timer. This gating mechanism represents a functional entity that regulates afferent input to the timer. The existence of a functionally separate gating mechanism in the modified model has been inferred from the differential effects of centrally active antitussive drugs on cough number and CTtot.

The modified model reflects this observation by showing that the timer (which also provides excitatory motor input to inspiratory and expiratory premotor elements) and inspiratory premotor activity are insensitive to the effects of centrally active antitussive drugs. Therefore, antitussive drugs must inhibit cough number by an action upstream from the timer. That is, they suppress the transmission of afferent input to the timer. Whether the gating mechanism represents a property of the second-order interneurons or some

- SAR: Pulmonary rapidly adapting receptor (RAR) second-order interneurons, which mediate afferent input from pulmonary RARs, may be suppressed by antitussive drugs. Permissive effect of pulmonary slowly adapting receptors (SARs) is represented by a facilitatory effect of pump cells on either the gate or pulmonary RARs. The gate regulates afferent input to the timer, and its suppression by antitussive drugs leads to a decrease in cough number. The timer regulates duration of the cough cycle and magnitude of inspiratory motor input to premotor elements. Pump cells, the timer, and inspiratory premotor activity are insensitive to the effects of antitussive drugs.
- I premotor: premotor-propriobulbar and bulbospinal inspiratory neurons; E premotor: premotor-propriobulbar and bulbospinal expiratory neurons.

![Fig. 5. Model for organization of central cough-generation system and the site of action of central antitussive drugs. Gray boxes represent elements that may be sensitive to antitussive drugs.](http://jap.physiology.org/)
undergoes a profound change in state from eupnea to cough. During mechanically induced cough, there is a very large increase in motor drive to inspiratory and expiratory muscles (30–32) due to a large increase in excitatory input from pulmonary RARs that is not present during eupnea. Furthermore, abdominal motor activity during cough has a decrementing pattern, unlike the typically augmenting pattern seen during eupnea (3). Therefore, it may not be appropriate to infer that the observations of Haxhiu and co-workers (17, 18) and the present results are due to an action of the drugs on common neural elements.

Although we show that medullary premotor expiratory pathways are sensitive to the effects of antitussive drugs, we cannot exclude an effect of one or more central drugs on expiratory spinal pathways. However, we know that any potential effect of these drugs on spinal motor drive related to cough would be limited to expiratory pathways, because diaphragm motor drive during cough was unaffected. Second, we also cannot exclude subtle effects of these drugs on other aspects of the cough motor pattern. Bolser and DeGennaro (6) showed in a model of fictive cough that intravenous administration of codeine disrupted coordination of inspiratory and expiratory motor drive during cough even at doses too low to inhibit the amplitudes of these bursts.

None of the drugs in the present study inhibited diaphragm EMG amplitude during spontaneous breathing and only CP-99,994 reduced respiratory cycle time (Ttot). The effect of CP-99,994 indicates that this drug increased respiratory frequency, which is consistent with a central excitatory effect on either the respiratory-pattern generator itself or an afferent system that alters its behavior. Both morphine and baclofen are known to be respiratory-depressant agents (2, 24). However, several reports in the guinea pig have shown that the doses of these drugs necessary for respiratory depression are greater than those required for inhibition of cough (2, 5, 19). These observations also are supported by the findings of May and Widdicombe (25) that codeine has no respiratory-depressant effect in dosage ranges that inhibit cough. The differences in dosages required for antitussive and respiratory-depressant activity of these drugs provide strong support for our model of a separate antitussive-sensitive gating system that regulates cough-related afferent input to the cycle timer. Given that Shannon and co-workers (27–29) have proposed that the cough and respiratory patterns are generated by a convergent system, the timer must be independent of the effects of antitussive drugs or respiratory depression would occur in concert with cough suppression.

We thank Drs. Paul W. Davenport, Bruce G. Lindsey, and Roger Shannon for their thoughtful contributions to the interpretation of the results. We also thank Frances DeGennaro and James McKenzie for excellent technical assistance.

This work was supported by the University of Florida and Schering-Plough Research Institute.

Address for reprint requests and other correspondence: D. C. Bolser, Dept. of Physiological Sciences, Box 100144, College of Veterinary Medicine, Univ. of Florida, Gainesville, FL 32610-0144 (E-mail: bolserd@mail.vetmed.ufl.edu).

Received 11 June 1998; accepted in final form 23 November 1998.

The transmission of afferent input to the timer is handled by second-order RAR interneurons and pump cells. Antitussive drugs could suppress the activity or action of one or both of these groups of interneurons. However, generalized suppression of second-order RAR interneuron activity is not consistent with the insensitivity of inspiratory motor activity to antitussive drugs. According to both models, suppression of second-order RAR interneuron activity would lead to inhibition of both premotor-propriobulbar and bulbospinal inspiratory and expiratory neuron activity during cough. Suppression of pump cell activity is unlikely to be responsible for our observations, because antitussive drugs had no effect on eupneic respiratory timing or integrated diaphragm EMG amplitude. That is, suppression of cough with central administration of antitussive drugs did not result in increased diaphragm EMG amplitude and inspiratory duration consistent with blockade of SAR afferent input to the respiratory-pattern generator.

These studies were conducted in animals anesthetized with pentobarbital sodium. This anesthetic can depress spontaneous expiratory abdominal and thoracic motor discharge (13–15). It is important to note that Warner et al. (34) have shown that the depressant effects of an induction dose of pentobarbital sodium on spontaneous expiratory muscle activity are transient, even in the face of constant plasma levels of this anesthetic. Furthermore, there is no evidence that pentobarbital sodium depresses expiratory motor discharge during cough. It is well known that cats anesthetized with pentobarbital sodium cough vigorously, with gastric or intrapleural pressures often well in excess of 100 cmH2O (23, 30). Indeed, we have routinely observed gastric pressures in excess of 130 cmH2O and tidal volumes 3–5 times eupneic levels during cough in cats anesthetized with pentobarbital sodium (Bolser, unpublished observations). The level of excitatory motor drive to expiratory motoneurons during cough is far greater than the level that is present during eupnea (3, 32) and probably overwhelms any depressant effect of the anesthetic.

Other investigators have shown that, during eupnea, abdominal motor discharge is more sensitive to central administration of drugs than is inspiratory motor discharge (17, 18). Indeed, abdominal motor discharge can be selectively enhanced by central administration of tachykinins or inhibited by a substance P antagonist (17). Our findings are consistent with the selective effects of drugs on expiratory motor discharge shown by Haxhiu and co-workers (17, 18). In particular, our results extend the work of those investigators by showing that tachykinin-receptor antagonists inhibit abdominal motor discharge during cough. However, it is important to note that the brain stem pattern generator undergoes a profound change in state from eupnea to cough. During mechanically induced cough, there is a very large increase in motor drive to inspiratory and expiratory muscles (30–32) due to a large increase in excitatory input from pulmonary RARs that is not present during eupnea. Furthermore, abdominal motor activity during cough has a decrementing pattern, unlike the typically augmenting pattern seen during eupnea (3). Therefore, it may not be appropriate to infer that the observations of Haxhiu and co-workers (17, 18) and the present results are due to an action of the drugs on common neural elements.

Although we show that medullary premotor expiratory pathways are sensitive to the effects of antitussive drugs, we cannot exclude an effect of one or more central drugs on expiratory spinal pathways. However, we know that any potential effect of these drugs on spinal motor drive related to cough would be limited to expiratory pathways, because diaphragm motor drive during cough was unaffected. Second, we also cannot exclude subtle effects of these drugs on other aspects of the cough motor pattern. Bolser and DeGennaro (6) showed in a model of fictive cough that intravenous administration of codeine disrupted coordination of inspiratory and expiratory motor drive during cough even at doses too low to inhibit the amplitudes of these bursts.

None of the drugs in the present study inhibited diaphragm EMG amplitude during spontaneous breathing and only CP-99,994 reduced respiratory cycle time (Ttot). The effect of CP-99,994 indicates that this drug increased respiratory frequency, which is consistent with a central excitatory effect on either the respiratory-pattern generator itself or an afferent system that alters its behavior. Both morphine and baclofen are known to be respiratory-depressant agents (2, 24). However, several reports in the guinea pig have shown that the doses of these drugs necessary for respiratory depression are greater than those required for inhibition of cough (2, 5, 19). These observations also are supported by the findings of May and Widdicombe (25) that codeine has no respiratory-depressant effect in dosage ranges that inhibit cough. The differences in dosages required for antitussive and respiratory-depressant activity of these drugs provide strong support for our model of a separate antitussive-sensitive gating system that regulates cough-related afferent input to the cycle timer. Given that Shannon and co-workers (27–29) have proposed that the cough and respiratory patterns are generated by a convergent system, the timer must be independent of the effects of antitussive drugs or respiratory depression would occur in concert with cough suppression.

We thank Drs. Paul W. Davenport, Bruce G. Lindsey, and Roger Shannon for their thoughtful contributions to the interpretation of the results. We also thank Frances DeGennaro and James McKenzie for excellent technical assistance.

This work was supported by the University of Florida and Schering-Plough Research Institute.

Address for reprint requests and other correspondence: D. C. Bolser, Dept. of Physiological Sciences, Box 100144, College of Veterinary Medicine, Univ. of Florida, Gainesville, FL 32610-0144 (E-mail: bolserd@mail.vetmed.ufl.edu).

Received 11 June 1998; accepted in final form 23 November 1998.
REFERENCES