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How does lobeline injected intravenously produce a cough?

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Abstract

In order to examine, whether the lobeline-induced cough is a true reflex or a voluntary effort to get rid of its irritating sensations in the upper respiratory tract, we systematically studied the cough response to lobeline, of subjects who were unable to make conscious discriminations i.e. were either comatose ($n = 4$) or anaesthetized ($n = 5$). 8 μg/kg lobeline injected into the right atrium of one and 29 μg/kg intravenously (i.v.) into another evenly and spontaneously breathing comatose subject produced a cough after 4 s and 12 s, respectively. Cough was repeatable and showed a dose response relationship i.e., its latency decreasing and its duration/intensity increasing with the dose. In a third subject, capable only of weak spontaneous respiration, a relatively high dose injected into the right atrium (44 μg/kg) generated a pronounced cough-like respiratory movement superimposed on the artificial ventilation and also during the apnoea after disconnecting the pump. No respiratory response was evoked in a fourth subject who had no evidence of brainstem reflexes. In five normals, cough was elicited with a mean dose of 35 ± 5 μg/kg i.v. (latency 14 ± 2 s; duration 10 ± 3 s). After thiopental anaesthesia, injecting 41 ± 7 μg/kg produced a cough within 13 ± 2 s that lasted for 12 ± 2 s. It may be noted that neither the later dose nor the latency or duration of cough that it produced were significantly different from the pre anaesthesia values ($P > 0.05$). These two sets of results show unequivocally that the lobeline-induced cough is evoked reflexely; its magnitude in the conscious state could vary by subjective influences. We discuss the likelihood of its origin from juxtapulmonary capillary receptors.

Keywords: J receptors; Hyperpnoea; Apnoea; Cough; Lobeline; Anaesthesia; Conscious effort; Left ventricular dysfunction; Cardiac output; Interstitial oedema; Pulmonary oedema

1. Introduction

The appearance of cough in response to injecting lobeline (3 mg) intravenously (i.v.) into humans has been known since 1934 (Robb and Weiss, 1934). Lobeline, an alkaloid extracted from the plant *lobelia inflata*,

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a well known respiratory stimulant has also recently been shown, to alter dopamine function (Dwoskin and Crooks, 2002). The cough with lobeline was assumed to have arisen by the stimulation of carotid chemoreceptors and the time of its appearance was used for determining the speed of circulation in a variety of patients with heart disease (Berliner, 1940; Bevan and Murray, 1963; Stern et al., 1966). Doses of lobeline, smaller than those that produce cough, have been noted to give rise to certain specific sensations in the mouth, throat and upper chest i.e. in the upper respiratory areas. These sensations are accompanied by respiratory reflexes consisting of an interruption of expiration or inspiration resulting in a brief apnoea which may be followed by a hyperpnoea or a vice versa of events (Bevan and Murray, 1963; Jain et al., 1972; Raj et al., 1995; Gandevia et al., 1998; Butler et al., 2001). Similar respiratory reflexes are also seen in anaesthetized animals (within 3.5 s in cats and dogs and in 1–2 s in rats) by stimulating their juxtapulmonary capillary (J) receptors by specific chemicals injected into the right atrium (Paintal, 1955, 1969; Sapru et al., 1981; Coleridge and Coleridge, 1984), or by stimuli such as pulmonary congestion or pulmonary oedema (Paintal, 1969; Coleridge and Coleridge, 1977). These pulmonary receptors are innervated by vagal endings −80% of which are non-myelinated or C fibres (conduction velocity less than 2.5 m/s) and the remaining 20% by A-delta or myelinated fibres; conduction velocity above 2.5 m/s (see, Anand, 2000b).

Lobeline injected rapidly (bolus) into the mid jugular vein of conscious, healthy horses also produces respiratory reflexes within 5–10 s, consisting of a hyperpnoea followed by an apnoea. In addition, in 15% of the horses it also gave rise to a cough consisting of a few episodes (Marlin et al., 2000). Cough was repeatable with the same dose and in the same horse (D.J. Marlin, personal communication) and no accompanying changes in dynamic lung compliance occurred indicating that lobeline produced these reflexes by bronchoconstriction. Although no neurophysiological studies are available that could identify the sensory receptors or mechanisms that give rise to these respiratory reflexes in horses, yet the route of lobeline injection and the short latency (see above) with which these effects appeared, strongly suggest that the pulmonary mechanisms involved are probably the same as those seen in other animals in response to injecting phenyl diguanide (PDG) (Paintal, 1969), capsaicin (Coleridge and Coleridge, 1984) or to an enkephalin-analogue (Sapru et al., 1981; Willette and Sapru, 1982). This is further supported by the presence of the expected inhibition of the viscersomatic activity, as after lobeline horses move less frequently (Marlin et al., 2000) and become very quiet and almost asleep (D.J. Marlin, personal communication). This is similar to the sudden cessation of walking seen in freely moving cats (Kalia et al., 1973) or to the impairment of coordinated motor activity in conscious rats into whom PDG is injected intravenously (Willette et al., 1982). In monkeys, the so-called respiratory artefact consisting of a deep inspiration at the end of the 'apnoea and rapid shallow breathing phase' seen in response to injecting lobeline i.v. (purported to stimulate J receptors), appears to be the beginning of a cough (Fig. 5B of Deep et al., 2001)—a conclusion also supported by the fact that the entire reflex is abolished by vagotomy (Fig. 7 of Deep et al., 2001).

In human subjects, since the respiratory reflexes occur almost simultaneously with the appearance of respiratory sensations, Raj et al. (1995) had concluded that the latter must also arise by stimulation of J receptors by lobeline. They supported this further, by demonstrating quite convincingly, that the rapidly adapting (RARs) and the slowly adapting (SARs) pulmonary stretch receptors i.e. the other major group of lung receptors, could not have contributed to these respiratory sensations or to the cough. Performing rapid, deep inspirations and expirations in order to stimulate RARs and a sustained hyperinflation, to stimulate SARs (both well established stimuli in animals), did not alter the intensity of lobeline-induced sensations felt by any one of the subjects. That, these respiratory sensations and reflexes including cough were of non-bronchial, but pulmonary vagal origin, was further revealed by Butler et al.'s (2001) study of patients who had *recently* received bilateral lung-transplants. Injecting lobeline i.v. into them, neither evoked respiratory reflexes including cough, nor did they report the characteristic respiratory sensations (Fig. 6 of Butler et al., 2001). Thus, these observations also rule out the origin of lobeline-cough, as believed earlier, from carotid chemoreceptors. Stimulating bronchial C fibre receptors in cats, does not give rise to any respiratory reflexes (Anand, 2000a). In man even if these