Blocking Action of Tetraethylammonium on Lobelin-Induced Thoracic Pain. (18608)

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The actions of tetraethylammonium (TEA) are complex. In general it blocks all the stimulatory nicotinic actions of acetylcholine (ACh) without interfering with the muscarinic effects of the drug. Thus it blocks the stimulatory action of ACh upon sympathetic and parasympathetic ganglion cells and upon motor end plates in skeletal muscles; presumably on this account it produces "ganglionic blockade" of motor autonomic fibers and depression at the neuromuscular junction. The effects of TEA upon the sensory system have been reviewed by Moe and Freyburger(1). Here again, TEA seems to act specifically upon sensory receptors stimulated by ACh (nicotinic action), nicotine or its congener, lobeline. Receptors so affected include some carotid and aortic chemoreceptors(2), those which initiate pilomotor and sudomotor cutaneous axone reflexes(3,4), and certain pain and position receptors(5).

We have observed another instance in which TEA blocks sensation. We have noted that lobeline, injected rapidly intravenously, for the purpose of measuring arm to aorta or carotid circulation time, usually produced substernal burning and distress associated with explosive cough within 8 seconds after injection. Since these sensations precede aortic or carotid chemoreceptor-induced hyperpnea by five to ten seconds, we believe that they are due to stimulation of sensory receptors supplied by the pulmonary circulation, probably in the pleura or respiratory tract. In the present study we have found that this type of chemically induced pain is susceptible to the blocking action of TEA.

We injected 5.0-7.5 mg of lobeline (free from preservative) into 7 patients who were to receive TEA for the treatment of peripheral vascular disease. In all except one, the dose was insufficient to cause hyperpnea. Six of these, however, experienced substernal burning discomfort, which disappeared in less than 2 minutes, and a paroxysm of coughing of about 30 seconds duration (Table I). After 10 to 15 minutes, each of these 6 was given 125-200 mg of TEA by slow intravenous injection. Ten to 15 minutes later, lobeline was repeated in dosage similar to or larger than that previously injected. This second injection produced either no reaction or a markedly diminished one. Since repeated injections of lobeline may result in paralysis of structures stimulated by earlier doses, we repeated the injection of lobeline in patient F. S. (Table I) without the intervening injection of TEA; there was no diminution in the burning sensation and cough.

Discussion. TEA does not seem to be an analgesic or narcotic in the usual sense of the word, since it does not relieve all types of pain, does not alter the threshold for burning pain, and does not alter reaction to pain or affect pain centers(5). When pain is due to increased activity of smooth muscle (in blood vessels or in the gastrointestinal tract) or of glands (gastric acid secreting glands), TEA produces relief by effecting autonomic blockade. However, some sensory receptors appear to be blocked directly and selectively by TEA. In all instances described to date (aortic and carotid chemoreceptors, cutaneous and thoracic receptors), these appear to be chemical receptors, all of which have the property of being stimulated by nicotine, lobeline or ACh.

We have been unable to localize these thor-

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3. Coon, J. M., and Rothman, S., *J. Pharm. Exp. and Therap.*, 1941, v73, 1.

4. Janowitz, H. and Grossman, M. I., *Science*, 1949, v109, 16.

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TABLE I.

Patient	1st inj. lobeline, mg	Response	TEA, mg	2nd inj. lobeline, mg	Response
E.M.	5	Coughing 2×. Substernal burning beginning in 11 sec.	200	5	Very slight burning in 50 sec.
A.	7	"Dry sensation of throat." Cough	175	7	None
M.I.	6	Pronounced cough. Substernal burning	150	6	No cough. Slight burning
A.D.	6	Substernal burning. Repeated coughing. Tachypnea	125	7	Cough one time 12 sec. None other
L.M.	7.5	Substernal oppression. Repeated cough	200	8	None
F.S.	6	Substernal burning. Paroxysmal coughing. Sulfur taste	125	7	Cough one time. Sulfur taste
F.S.	6	Substernal burning. Paroxysmal coughing	—	6	Substernal burning. Paroxysmal coughing

acic receptors. Experiments performed upon lightly narcotized dogs, in which lobeline was injected into the pleural cavity, the peritoneum or pulmonary artery or sprayed into the trachea, have not been rewarding because of the lack of objective indications of the experience of pain. Analogous studies have not been attempted in man.

Nevertheless, we suggest tentatively that the receptors may be in the visceral pleura because of two previous observations: (a) McLaughlin(6) has reported the presence in the visceral pleura of the cat of specialized cells which bear a strong resemblance to Pacinian corpuscles in the mesentery; it is known that the latter are stimulated by nicotine(7) and therefore presumably by its congener, lobeline. (b) Israel and associates(8) have observed that some types of pleural pain are relieved promptly by the intravenous injection of TEA.

We do not know what might constitute the natural stimulus to these receptors though we suspect that it is chemical (local chemical products of inflammation or of metabolism) rather than mechanical. However, TEA seems to have the property of blocking these receptors selectively without interfering with adjacent sensory receptors in the chest wall.

Direct proof of the hypothesis that these are pleural receptors would require that characteristic pleural pain be reproduced by the injection of a chemical excitant into the pleural cavity and be blocked by TEA administered by the same route. This we have not attempted in man.

Summary. The hypothesis is offered that specialized pain receptors exist in the visceral or parietal pleura and that TEA relieves certain types of thoracic pain by blocking these receptors. Attempts to demonstrate these receptors in lightly narcotized animals have been unsuccessful. However, it has been demonstrated that lobeline injected intravenously into man will produce substernal burning and coughing, which can be blocked by the prior injection of TEA. The significance of these observations is discussed.

6. McLaughlin, A. I. G., *J. Physiol.*, 1933, v80, 101.

7. Brown, G. L. and Gray, J. A. B., *J. Physiol.*, 1948, v107, 306.

8. Israel, H. L., Keeter, E. L., Urbach, F. E., and Willis, W. D., *N. Eng. J. Med.*, 1949, v241, 738.

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