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CHANGES IN PULMONARY MECHANICS INDUCED BY MELATONIN*

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Recently Lerner et al. (1) isolated a substance from the pineal body called melatonin (5-methoxy-N-acetyltryptamine). This substance is synthetized in the pineal gland enzymatically from serotonin (5-hydroxy-tryptamine) (2, 3). Among its physiological and pharmacological actions melatonin is known to bleach the skin of the frog when applied locally (1), to inhibit spontaneous contractions of rat intestine and uterine smooth muscle (4, 5), to abolish 5-hydroxytryptamine-induced contraction in these preparations and to decrease the excitability of the frog sciatic nerve (6).

In view of these findings it seemed of interest to examine the action of melatonin on pulmonary mechanics, since resistance to air flow is determined mainly by the activity of the bronchial smooth muscle.

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The present paper describes the response of the bronchi to melatonin in normal intact animals and of bronchi with increased tonus after 5-hydroxytryptamine administration. The possible mode of action of this substance is discussed.

Materials and Methods

Mongrel dogs were anesthetized with sodium penthotal administered intravenously. Total lung resistance (TLR) and lung compliance (C_L) were determined by the method of Mead and Whittenberger (7) using an intrapleural catheter and measuring flow, volume and pressure, each recorded on a four channel Sanborn M 150 recorder. Air flow was measured with a Sanborn pneumotachograph and Statham differential pressure transducer, and the volume signal was obtained by integration of the flow signal. The transpulmonary pressure (TPP) was measured with a Statham differential pressure transducer one side of which was connected to the intrapleural catheter and the other side to the tracheal cannula. The output of the above parameters were also connected to a cathode ray oscilloscope and a pressure-volume trace was obtained. Electronically, a voltage proportional to the pressure needed to overcome the airway resistance was subtracted from the pressure-volume trace until a straight line resulted. The slope of this line represented C_L, and from the applied voltage the TLR was calculated.

Fifty nine experiments in eleven dogs were performed. Pulmonary mechanics were studied during a control stage and following intravenous administration of melatonin (Regis Chemical Co., Chicago Ill.) or 5-hydroxytryptamine (Light Chemical Co. Ltd., Colnbrook, England).

In part of the experiments, melatonin was administered first, and in other experiments melatonin was given after two successive intravenous injections of 5-hydroxytryptamine, and finally the response of the bronchial smooth muscle to 5-hydroxytryptamine was tested again. These experiments were repeated after bilateral cervical vagotomy.

Results

1. Effect of melatonin on total lung resistance and lung compliance.

After intravenous administration of melatonin (60×10^{-6} moles/kg) into a peripheral vein, a definite decrease in TLR was observed with a concomittant increase in C_L. This effect was of short duration (Fig. 1). The degree of bronchodilatory action of melatonin was inversely proportional to the initial tonus of the bronchial smooth muscle.

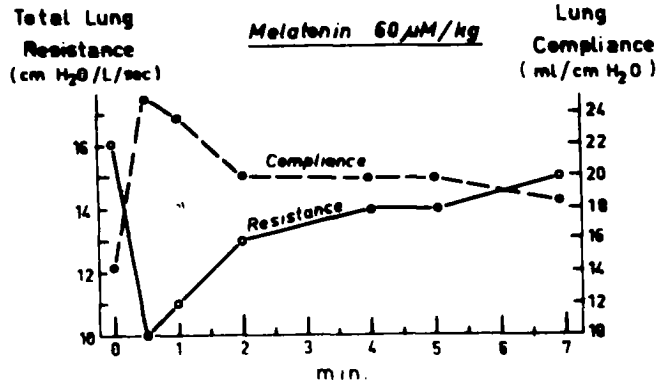

Fig. 1

Effect of melatonin (at 0') on total lung resistance and lung compliance

2. Inhibition of 5-hydroxytryptamine-induced bronchoconstriction by melatonin.

Administration of 5-hydroxytryptamine (10^{-6} moles/kg) caused

a severe bronchoconstriction. After the TLR returned to control value, melatonin was injected followed by 5-hydroxytryptamine administration at different time intervals. Melatonin caused a prominent inhibition of 5-hydroxytryptamine induced bronchoconstriction and its action lasted up to 90 minutes (Fig. 2). In a control experiment, no tachyphylaxis was observed after seven successive intravenous injections of 5-hydroxytryptamine.

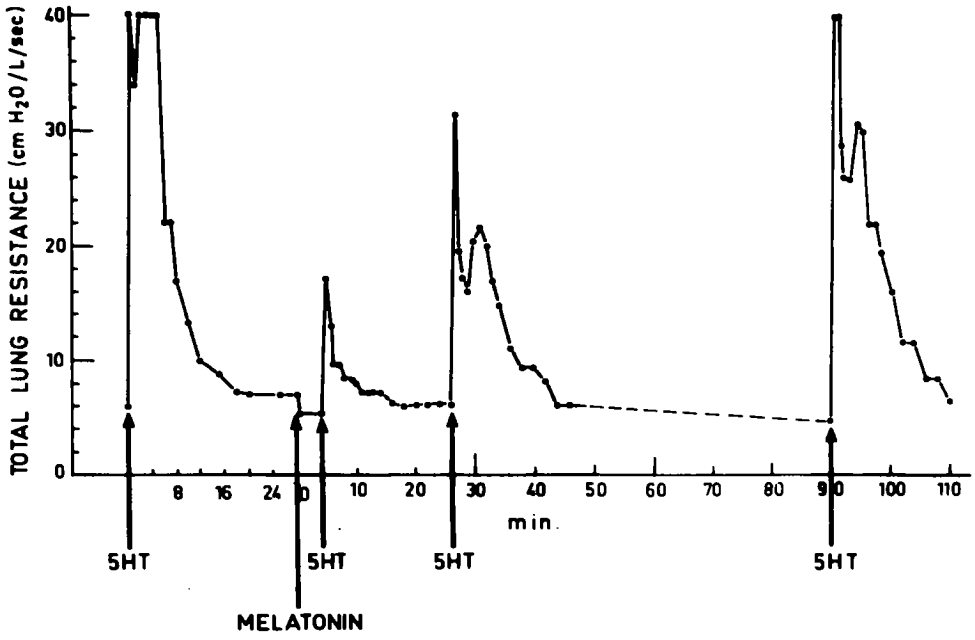

FIG. 2

The bronchoconstrictory effect of 5-hydroxytryptamine before and different periods after administration of melatonin in intact dog.

3. Inhibition of 5-hydroxytryptamine induced bronchoconstriction by melatonin after bilateral vagotomy.

After vagotomy 5-hydroxytryptamine in the same dose (10^{-6} moles/kg), caused a smaller bronchoconstriction. Melatonin inhibited this effect, although the time course was much shorter (Fig. 3).

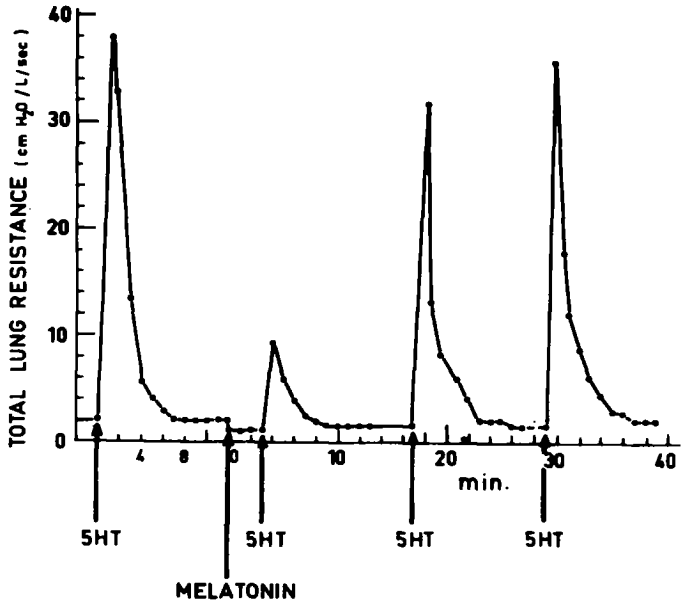

FIG. 3

The bronchoconstrictory effect of 5-hydroxytryptamine before and different periods after administration of melatonin in bilateral cervical vagotomized dog.

Discussion

In the past, the effects of melatonin on excitable tissues were studied on isolated organs and therefore only the local inhibitory action of this substance was observed. In the present work, the effects of melatonin on smooth muscle were examined in vivo and therefore the local, as well as the indirect action or both could be evaluated. In order to differentiate the various actions of melatonin, the experiments were repeated in the intact animal also after bilateral cervical vagotomy.

Our results demonstrate clearly a bronchodilator effect of melatonin in the intact animal, as well as a marked inhibitory action of this substance upon 5-hydroxytryptamine induced bronchoconstriction. This effect of melatonin was persistent even after vagotomy and therefore a

local action must be implied. The time course of the melatonin effect after vagotomy differs from that in the intact animals, i.e., the melatonin has both local and indirect action on the bronchial smooth muscle.

Since the concentrations of melatonin used in our experiments were large, it is difficult to assess the physiological importance of melatonin in regulation of bronchial smooth muscle activity.

Summary

The effect of melatonin, a substance isolated from the pineal body, was examined on the pulmonary mechanics of intact dogs before and after vagotomy. The following results were obtained:

1. A decrease in total lung resistance;
2. An increase in lung compliance;
3. Inhibition of 5-hydroxytryptamine induced bronchoconstriction;
4. The bronchodilation and inhibition are most probably caused by local and indirect action of melatonin on the bronchial smooth muscle.

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