INTRODUCTION

During exercise, minute ventilation (VE) in man increases manifold. This increase can not be explained only by changes in blood parameters (pHa, Paco2 and Paoz) known to play a crucial part in the control of ventilation under resting conditions. An increase in arterial plasma potassium ([K+]a) from ca. 4 mM to 7-8 mM has been found during exercise (Medbo & Sejersted, 1990). Studies by several investigators suggest that the potassium ion most likely plays a part in the increase of VE during exercise. Supporting these findings are results from intravenous infusions of KCl into anesthetised cats which have been shown to stimulate arterial chemoreceptors and induce ventilation (Linton & Band, 1985). Also, studies on muscle afferents known to stimulate VE have shown that raised extracellular potassium concentration stimulates types HI and IV afferents, especially group IV. Although studied in different species, the effects of raising [K+]a in rats has not been investigated.

The accumulation of lactate and the accompanying decline in pHa during metabolic acidosis while performing strenuous exercise has been known for many years and has been associated with the extra drive in VE observed above the lactate threshold (Wasserman et al., 1973). Little or no attention has been given to the possible role of the lactate ion itself (Lac-) on the control of VE. Results from studies of the effect of Lac- on muscle afferents did not reveal any effect of the ion on the sensory neurones. In other experiments, in which sustained venous infusions of lactate were applied, both pHa and VE were significantly altered. The possibility that Lac- could independently influence minute ventilation was not considered.

Therefore, we wanted to study whether raising the arterial lactate ion concentration without changing the pHa would affect ventilation. We used the anesthetized rat as a model, in which we increased both the K+ and Lac- concentration by venous infusions. The aims of this study were therefore threefold: 1) to investigate the effect of sustained hyperkalemia on VE; 2) to test the hypothesis that the lactate ion had an independent effect on VE; and 3) to compare the effect of these two variables on VE.

METHODS

We used fourteen male rats (350-450g) which were randomly divided into four separate experimental groups; KC1 and Lac" groups and two control groups. In the beginning of each experiment the rat was anaesthetized, tracheotomized and prepared with catheters in the tail artery, left femoral artery and vein. Core temperature was measured and maintained at 38°C. Either KC1 or lactate solutions were infused in anesthetized spontaneously breathing Wistar rats to raise the respective ion arterial concentration gradually to levels similar to those as observed during strenuous exercise. Ventilation (VE), blood pressure and heart rate were, recorded continuously and arterial [K+], [Lac*], pH and blood gases were repeatedly measured from blood samples. To prevent changes in pH during lactate infusions, a solution containing mixture of sodium lactate and lactic acid was infused.

RESULTS

Raising [K+] from 4.2 ±0.10 (SE) to 7.8 ±0.11 mM increased VE 20.3 ±5.28% without changes in pH or PCO2- Raising [Lac-] from 0.80 ± 0.2 to 13.2 ±0.6 mM induced an increase in ventilation 47.0 ±4.0% without any concomitant changes in either pH or PCO2- The correlation coefficient (r) for the relationship between the arterial potassium and lactate concentrations and ventilation was. 0.80 (p<0.01) and 0.89 (p<0.01) respectively. The ventilatory increase was significantly higher (p<0.01) in the lactate group compared to the potassium group. The comparison between the two experimental groups was made after 10 min of infusion when the arterial concentration had reached levels similar to those as seen during severe exercise. In addition, the two experimental groups differed in
respective to changes in their arterial blood gas concentration. The potassium group showed no significant changes in either Pa\textsubscript{o}2 or Paco\textsubscript{2}. However, the lactate group showed a significant increase in Pa\textsubscript{o}2 but not in Paco\textsubscript{2}.

**DISCUSSION**

The main findings of the present study are that: 1) sustained hyperkalemia raises VE in rats, 2) Lac\textsuperscript{-} stimulates VE in spite of a normal pH\textsubscript{a} and 3) the Lac\textsuperscript{-} is a more potent stimulus to VE than K\textsuperscript{+}. The approximate 20% increase observed in VE during the infusion of KC\textsubscript{l} occurs within 10 min and at the same time [K\textsuperscript{+}]\textsubscript{a} reaches values seen in strenuous exercise in men. Compared to previous experiments in other species in which venous infusions of KC\textsubscript{l} have been used the increase in VE in the present study was moderate. Although the change in Paco\textsubscript{2} did not differ significantly between the KC\textsubscript{l}-group and its control group there was a clear tendency for a decrease in Paco\textsubscript{2} from the preinfusion level in the KCl-group. This hypocapnic breaking thus most likely diminishes the stimulatory effects of K\textsuperscript{+}. Therefore, it is most likely that K\textsuperscript{+} is responsible for stimulating the hyperventilation and producing the observed hypocapnia in the animals models thus far studied.

The primary new finding of this study is that the lactate-ion infusion stimulates VE without any changes in pH\textsubscript{a} or Paco\textsubscript{2}. Although the increase in VE persists up to [Lac\textsuperscript{-}]\textsubscript{a} = 30 mM, physiological limits were reached in about 10 min, resulting in a 47% increase in VE. Other authors have studied the effect of intravenous infusions of lactic acid on VE. These authors did not discuss the possibility of whether Lac- may have a role in stimulating ventilation, as our results indicate, and they made no attempt to prevent changes in pH\textsubscript{a} in their animal models as in the present study.

The cause-and-effect relationship between the metabolic acidosis and hyperventilation in heavy exercise in humans, suggested by Wasserman *et al.* (1973), has been questioned. It has been pointed out that possibly neither humans nor rats depend significantly on metabolic acidosis as the critical stimulus for hyperventilation during exercise (Fregosi & Dempsey, 1984). Our results show that the Lac-\textsuperscript{-} has a stimulatory effect on VE which can not be explained by an increase in [H\textsuperscript{+}]\textsubscript{a}. This suggests that the Lac-\textsuperscript{-} is stimulating VE but not H\textsuperscript{+}. By what mechanism Lac-\textsuperscript{-} affects VE is difficult to speculate. The observed isocapnea shows that there is a balance between CO\textsubscript{2} production and CO\textsubscript{2} elimination by breathing. This agrees with the known strong correlation between V\textsubscript{o}2 and VE during exercise.

Although our results suggest that in rats Lac-\textsuperscript{-} is a more potent ventilatory stimulant than K\textsuperscript{+}, it is important to recognise that the [K\textsuperscript{+}]\textsubscript{a} increases gradually during incremental exercise. The accumulation of [Lac\textsuperscript{-}]\textsubscript{a}, on the other hand, is only observed during severe exercise and therefore could only contribute to an increase in VE over the lactate threshold and/or to a sustained high VE during the recovery period.

The present study shows that lactate can stimulate ventilation without any accompanying changes, either in pH\textsubscript{a} or Paco\textsubscript{2}. This finding further supports the notion that [H\textsuperscript{+}]\textsubscript{a} may not be as important in stimulating hyperventilation observed in heavy exercise as previously thought. The possibility that the Lac-\textsuperscript{-} ion may be even more important is suggested by the present study.

This study was supported by The Icelandic Research Fund for Graduate students (Th.H), the Icelandic Council of Science (J.O.S.) and the University of Iceland Research Foundation (J.O.S.).

**REFERENCES**


