The Effect of Sevoflurane on Rat Liver Mitochondrial Respiration

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The effect of sevoflurane on rat liver mitochondrial respiration has been investigated with a Clark type oxygen electrode at 25°C, pH 7.4. The higher susceptibility of NADH-linked substrate (glutamate) oxidation (with respect to succinate oxidation) to the damages by sevoflurane has been confirmed. (Key words: sevoflurane, rat liver mitochondria, oxygen consumption)

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Text

Some inhalational anesthetics are known to induce alterations of the mitochondrial energy-converting processes which consists of the electron transport system and oxydative phosphorylation[1]. The former one is further divided into four submitochondrial complexes. Complex I is termed the NADH dehydrogenase system and fascilitates the flow of electrons from NADH to coenzyme Q. Complex II is the succinate dehydrogenase system and transfers electrons from succinate to coenzyme Q. Complex III consists of cytochromes b and c_1 and permits transfer of electrons from coenzyme Q to cytochrome c. The terminal complex IV enables electrons to pass from cytochrome c to molecular oxygen. In the respiratory chain there are three sites where the pumping of protons and the production of ATP (oxidative phosphorylation) occur. Site 1 is between NADH and coenzyme Q, site 2 is between cytochrome b and cytochrome c, and site 3 is between cytochrome c and oxygen. Each of these sites yields one ATP via proton pumping. The oxidation of NADH yields three molecules of ATP per atom of oxygen reduced (a phosphorylation/oxygen uptake ratio: P/O ratio, of 3), but succinate dehydrogenase produces $FADH_2$, which reacts with coenzyme Q with a P/O ratio of 2.

Regarding the volatile anesthetics, halothane, for example, inhibits the state 3 respiration of glutamate and, also, at the lesser degree, of succinate[2]. This indicates that halothane probably acts on NADH-dehydrogenase[3,4]. Miller et al.[5] also confirmed the inhibition of the ADP-stimulated respiration in the presence of NAD-linked substrates by halothane, but not in the presence of succinate. Moreover these authors reported an alteration of membrane permeability

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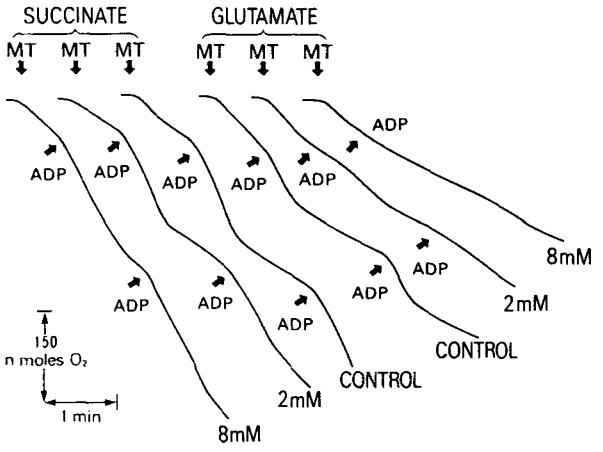

Effect of 2mM and 8mM sevoflurane on succinate and glutamate oxidation by mitochondria

Fig.

in the presence of halothane. Depression on the NAD-linked substrate oxidation has also been demonstrated with volatile anesthetics such as diethylether, methoxyflurane, enflurane and isoflurane[6–8].

In view of the reported results, sevoflurane seems to extert the same effects as other volatile anesthetics on the mitochondrial respiration. Therefore, the effects of sevoflurane on the mitochondrial respiration were investigated and the following results were obtained.

Male Wister strain rats were killed by decapitation. The liver was immediately removed and mitochondria were prepared using the method of Schneider et al.[9]. The protein content of mitochondrial pellet was assayed according to Lowry et al.[10] The mitochondrial oxygen consumption was measured with a Clark type oxygen electrode[11] in the medium which consited of 0.3M sucrose, 20 mM Tris-HCl (pH 7.4), 20 mM $MgCl_2$, 20 mM K-phosphate, and 5 mM glutamate or 5 mM succinate at 25°C.

The figure illustrates the effect of sevoflurane on mitochondrial respiration. The arrows indicate the additons of mitochondrial pellet (MT) and 0.16 mM of ADP which initiate maximum oxygen consumption of mitochondria (ADP-stimulated respiration). ADP-unstimulated respiration occurs when ADP is completely consumed and usually follows ADP-stimulated one.

When glutamate was employed as the substrate, inhibited and prolonged ADP-stimulated respiration was observed in the presence of both 2 mM and 8 mM sevoflurane as compared to the control one. On the other hand, employing succinate as the substrate, ADP-stimulated and ADP-unstimulated respiratory curve in the presence of 2 mM sevoflurane was simular to the sevoflurane free respiratory curve. In 8 mM sevoflurane, ADP-stimulated respiration was enhanced and ADP-unstimulated respiration was uncoupled. This means that the respiratory control ratio was remarkably declined and a general uncoupling of oxidative phosphorylation was obtained. Our results were not in accord with the inhibition of succinate respiration reported by Snodgrass et al.[2] but with Vincenti et al.[8]. As demonstrated by the decline of glutamate oxidation, a marked depression at NADH-dehydrogenase level was observed. The high rate of respiratory

control with succinate in the presence of sevoflurane suggests that the ATP-synthetase and the electron transport of complexes II and III are still working well.

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