TITLE: INTRACORONARY INFUSION OF ATP ATTENUATES RENAL SYMPATHETIC NERVE ACTIVITY MEDIATED BY VENTRICULAR BARORECEPTORS

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ATP has gained popularity as a hypotensive agent. It has been demonstrated that renal sympathetic nerve activity (RSNA) increases dose-dependently at lower doses of ATP because of hypotension induced arterial baroreflex activity, but RSNA decreases at higher doses despite further reduction of mean arterial pressure (MAP).[1] The purpose of this study was to determine the mechanism by which the high doses of ATP suppress RSNA.

Mongrel dogs were anesthetized with alpha-chloralose, intubated and mechanically ventilated with oxygen. Thoracotomy was performed and a 27 ga hypodermic needle was inserted into the left circumflex coronary artery. The left renal sympathetic nerves were isolated and placed on a bipolar silver electrode for measurement of RSNA. Dose response effects of intracoronary (IC) or intravenous (IV) infusion of ATP (100, 200, 400 µg/kg/min) for 5 min on % change of RSNA and MAP were studied in intact and vagotomized dogs.

RSNA was increased dose-dependently with decreasing MAP during the ATP- IV infusion (Fig 1.2). Elevation of RSNA was attenuated by the higher ATP-IC infusion rates (Fig 1), despite the fact that MAP decreased dose-dependently (Fig 2). This suppression of RSNA by the ATP-IC infusion was completely abolished by the bilateral vagotomy (Fig 3). The level of MAP with ATP-IC infusion was significantly lower than that with ATP-IV infusion (Fig 2). After vagotomy, the level of MAP between the ATP-IC and ATP-IV infusion became identical (Fig 4).

Ventricular baroreceptors are located mainly throughout the left ventricle and are associated with cardiac vagal afferent pathway[2]. This study clearly demonstrated that infusion of larger doses of ATP into the left circumflex coronary artery inhibited RSNA due to cardiac vagal afferent mechanisms. It is speculated that IV infused ATP could not reach the coronary circulation to affect the ventricular baroreceptors, since ATP is immediately metabolized to adenosine immediately in the blood stream. The reduction of MAP was greater with ATP-IC infusion in intact dogs due to decreased sympathetic outflow in addition to the direct vasodilatory effect of ATP. The results indicate that larger doses of ATP suppress reflex sympathetic activity via the ventricular baroreceptors with cardiac vagal afferent pathway.

References: 1. ANESTHESIOLOGY 71: A58 1989
2.Circulatory Physiology: pp153-176 1984.

Fig 1. Intact

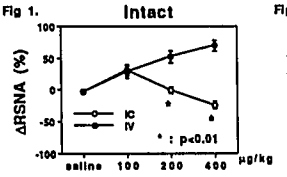


Fig 3. Vagotomy

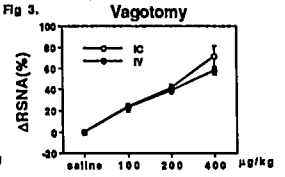


Fig 2. Intact

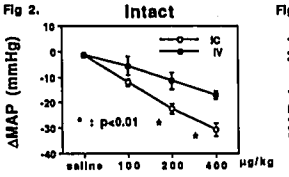
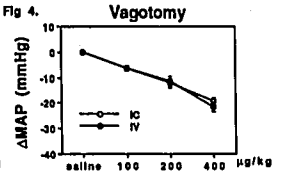


Fig 4. Vagotomy



Statistical analysis: ANOVA followed by Newman-Keuls' Method.
n=7 for each group

Title : EFFECTS OF PROPOFOL ON MITOCHONDRIAL OXIDATIVE PHOSPHORYLATION IN RAT LIVER

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Many anesthetics have been shown to impair mitochondrial functions such as oxygen consumption or ATP synthesis[1] . However, propofol effects on mitochondria remains to be investigated.

The goal of this study was to assess the effects of propofol (P), in clinical range of concentration (0-750 µM, 0-125 µg/ml), on the oxidative phosphorylation of rat liver mitochondria.

This study was approved by the Animal Welfare Commitee. Mitochondria were isolated from rat liver by differential centrifugation. Mitochondrial Oxygen Consumption Rate (MOCR) was measured at 28°C, using a Clarck electrode. ATP synthesis (ATP syn) was measured by incorporation of 32 P-phosphate.

Fig 1 shows a biphasic effect of P on mitochondrial oxygen consumption. Stimulation of mitochondrial respiration induced by P at low concentrations (<42 µg/ml) resulted from its uncoupling effect. At the highest concentrations (> 67 µg/ml) P inhibited the respiratory chain. These effects lead to ATP syn inhibition; our data show that the maximum effect was obtained at 300 µM (fig 2). These ATP syn inhibitory effects result from uncoupling effect of P because the maximum stimulation of MOCR leads to the maximum ATP syn inhibition.

Our data demonstrate that propofol, in a range of clinical concentrations (50-100 µM, 8-17 µg/ml), have uncoupling properties. At high concentration (> 67 µg/ml), P is an inhibitor of respiratory chain. Finally, in patients, P may increase oxygen consumption and decrease energetic reserve.

1 Proc. Nat. Acad. Sci : 80 : 3313-17 1983

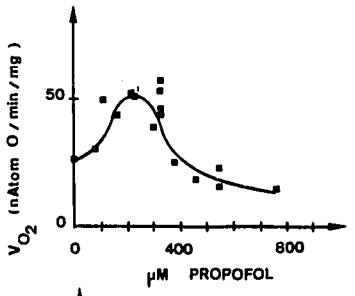

Fig 1 : Oxygen Consumption vs. Propofol Concentration

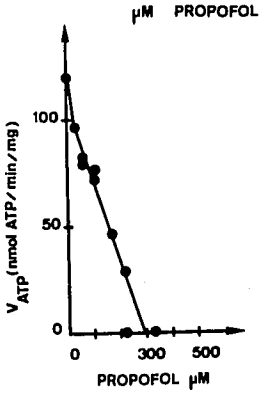

Fig 2 : ATP Synthesis vs. Propofol Concentration