CARDIOVASCULAR AND RESPIRATORY EFFECTS OF PIPERINE

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ABSTRACT

Cardiovascular responses to intravenous administration of piperine were investigated in both conscious and unconscious rats. In anesthetized animals, intravenous injection of a low dose of piperine (0.4 mg/kg body weight) caused a transient drop in blood pressure and bradycardia. Piperine at higher doses (0.6-1.0 mg/kg body weight) also caused a transient drop in blood pressure, bradycardia and was followed by a complex pattern of overshoot of blood pressure, another drop, then a gradual return to normal. However, when equivalent volumes of solvent alone were tested, an early transient hypotension and bradycardia were also observed. This magnitude of the early hypotension after solvent alone could not be statistically differentiated from the effect of piperine.

These results suggest that the anesthetized rat may not be the ideal animal model for studying the cardiovascular effects of piperine in saline-DMSO-ethanol. The effects of piperine were then measured in awake rats. Animals were prepared by first implanting heparin-treated cannulas into carotid artery and jugular vein. They were then allowed to recover overnight.

In conscious rats, the cardiovascular responses to piperine were found to be similar to those in anesthetized rats, except that following the hypotension, with 0.4 mg/kg, blood pressure gradually returned to control levels, while at higher doses, there was an overshoot followed by
a return to normal. There was no second drop in blood pressure. In contrast to the anesthetized rats, solvent effect was negligible. Therefore, the specific piperine effects in these animals were more clearly observable.

In conscious animals, the quantitative effects on respiratory system were also measured as well as the cardiovascular parameters. In awake animals, the ventilatory response to intravenous piperine was studied without the additional influence of anesthetics or surgical alteration of the respiratory passage. Respiratory rate ($f_r$), tidal volume ($V_t$), and minute volume ($\dot{V}_t$) were measured by using the barometric method. Intravenous piperine (0.4 to 0.8 mg/kg BW) induced a period of apnea in proportion to the dose given. 1 mg/kg BW, however, produced a variable duration of apnea. In the lower dose range of intravenous piperine, 0.4 to 0.6 mg/kg administration of the drug produced a period of apnea followed by a resumption of breathing at a reduced respiratory rate post-apnea followed by a transient hyperpnea. The extent to which post apneic $f_r$ was reduced varied in a dose-related manner. On the other hand following the apnea, $V_t$ was markedly increased. Thus, despite the lower $f_r$, the elevated $V_t$ resulted in a higher minute volume, $\dot{V}_t$ post apnea. This result suggests that the increment in $V_t$ and thus $\dot{V}_t$ was a compensatory response, proportional to the duration of apnea. In contrast, the breathing response in the higher dose range of piperine, 0.8 to 1.0 mg/kg was a $\dot{V}_t$ post apnea which was lower than normal, and increased with time to exceed the pre-piperine level.

Mechanism of action of piperine was investigated. Bilateral vagotomy which was performed in anesthetized rats could completely abolish the initial drop of blood pressure, bradycardia and significantly diminished the duration of apnea. Both atropine (0.2 mg/kg) and hexamethonium ion
(1 mg/kg) could significantly diminish the initial drop of blood pressure and bradycardia whereas it had no effect on duration of apnea in anesthetized rats. However, in conscious rats, atropine at the same dose could significantly diminish the duration of apnea. At least, the results indicate that the initial drop of blood pressure, bradycardia and apnea is mediated mainly via the vagus nerve, whereas the second drop of blood pressure (in anesthetized animals) was suggested to be mediated mainly via vasodilatation.

Regarding the pressor effect of piperine, neither bilateral vagotomy nor atropine, phentolamine, yohimbine, propranolol or hexamethonium ion could abolish the pressor effect of piperine. Only verapamil could completely block the pressor effect of piperine. Pretreatment with atropine and verapamil was found to completely block all the cardiovascular and respiratory effects of piperine. These findings suggest that the pressor effect of piperine is intimately related to the influx of Ca^{++} by some other mechanisms rather than adrenergic activation.