ISOMERS' INTERACTION OF ISOPROTERENOL IN THEIR PROPER ACTIONS ON THE CARDIAC BETA-ADRENOCEPTORS IN VIVO AND IN VITRO.

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We have argued that there may be an interaction between the (−) and (+) isoproterenol at the level of beta-adrenoceptors and/or the pharmacokinetics. In order to investigate this possibility, the cardiac responses to (−) isoproterenol were studied in the absence and presence of (+) isomer *in vivo* and *in vitro* using guinea pigs, and were compared with those to (±) isoproterenol.

Aerosol inhalation of 0.25% (−) isoproterenol induced the increase of heart rate (HR) and decrease of diastolic blood pressure (DBP), and cardiovascular responses to (−) isoproterenol were not significantly different from those to corresponding dose (0.5%) of (±) isoproterenol. In contrast, aerosol inhalation of 0.25% (+) isoproterenol induced a slight cardiovascular responses but there was no significant difference between the cardiovascular responses to 0.25% (+) isoproterenol and saline inhalations. The cardiovascular responses to 0.25% (−) isoproterenol inhalation were not affected by the concomitant presence of 0.25% (+) isomer. However, prior inhalation of 0.25% (+) isomer reduced the increase response of HR but not the decrease response of DBP to aerosol 0.25% (−) isoproterenol. Furthermore, the increase response of HR to intravenously administered (±) isoproterenol (1 ug/kg) was also reduced by prior inhalation of 0.25% (+) isoproterenol. In isolated atria, the concentration-response curves and EC_{50} values for positive chronotropic and inotropic responses to (−) and (±) isoproterenol were not significantly different, and as was the case *in vivo*, the cardiac stimulating potency of (−) isomer was not significantly affected by the presence of (+) isomer which was 30-fold less potent than (−) isomer in the isolated atria from guinea pigs.

The above results suggest that the prior inhalation of (+) isoproterenol reduces the cardiac responses to aerosol (−) isoproterenol which may result from desensitization rather than antagonism at the cardiac beta-adrenoceptors by (+) isoproterenol. Further mechanism of the cardiac hyporesponsiveness to (−) isoproterenol by the prior treatment of (+) isoproterenol remains to be elucidated.