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EFFECTS OF VERAPAMIL, PAPAVERINE, SODIUM NITRITE, AND HYDRALAZINE ON ETHYL ALCOHOL-INDUCED CONTRACTION OF THE ISOLATED HUMAN UMBILICAL ARTERY*

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The effects of vasoconstrictor agents such as serotonin[1,2], noradrenaline[3], bradykinin, histamine, some prostaglandins, KCl[4] and some sympathomimetic drugs having a beta-mimetic effect such as adrenaline and isoprenaline[5] on human umbilical arteries have been studied. There have been relatively few investigations regarding the pharmacodynamic effects of ethyl alcohol on the same arterial bed[6,7].

It is well-known that chronic ingestion of alcohol during pregnancy may result in the fetal alcohol syndrome characterized by prenatal and postnatal growth retardation, central nervous system abnormalities and facial dismorphology in the fetus[8-11]. It has been affirmed that the impairment of essential amino acids and oxygen transport to the fetus result in this syndrome[12,13]. However, it has been demonstrated in a recent study that when a high dose of alcohol is infused into a monkey, the umbilical arteries temporarily contract, and the umbilical circulation becomes insufficient leading to severe hypoxia in the fetus[14]. Besides, it has also been demonstrated by Altura et al[7], that in vitro ethyl alcohol has a vasoconstrictor effect on the umbilical arteries. In order to eliminate this vasoconstrictor effect, they studied the effects of some antagonists such as phentolamine, methysergide, pyrilamine, metiamide, atropine, propranolol and indomethacin and proved that they are ineffective. In this study, various antagonists such as verapamil, papaverine, sodium nitrite and hydralazine have been used to inhibit ethyl alcohol-induced contraction of human umbilical arteries in vitro.

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Material and Methods

We used umbilical arteries isolated from cords obtained from the Konya Maternity Hospital in this study. The cords from caesarean sections and anesthetized cases were not utilized. Precautions were taken to eliminate cords belonging to subjects exhibiting eclampsia, hypertension, diabetes mellitus, Rh factor incompatibility and from mothers on medication (antihistamines, meperidine, adrenergic blockers, anticholinergics) during their last two months of pregnancy. The vessels were dissected free of connective tissue and cut spirally into strips approximately 2-3 mm in width and divided into segments measuring 20-25 mm in length. Each strip was mounted vertically in an organ bath containing 25 ml of Krebs-Henseleit solution. The resting tension was adjusted to 1 g and the segments were allowed to relax for a period of two hours during which the bathing fluid was changed every 15 minutes. The solution was maintained at 36-38°C and bubbled with a gas mixture containing 95% oxygen and 5% carbon dioxide. Responses to drugs were isometrically recorded by means of a transducer (Harvard Universal Oscillograph). At the end of the resting period, the preparations were treated with a high K^+ (80 mM) solution obtained by replacing 80 mM NaCl with an equimolar quantity of KCl. The tissue was relaxed by washing with fresh solution. Following this process, a cumulative dose-response curve to ethyl alcohol was obtained, and the tissue was washed again. The same procedure was repeated in the presence of 10^{-6} M concentration of antagonists. An antagonist was incubated for 30 minutes at a given concentration, and only one antagonist was tested on each strip. The responses to ethyl alcohol before and after the addition of antagonists were considered the percentage value of KCl-induced contraction. Maximum relaxations caused by antagonists and EC_{50} values (the concentration producing 50% of the maximum response) of ethyl alcohol were also calculated. A Krebs-Henseleit solution of the following composition (mM) was used: NaCl 118, KCl 4.70, $CaCl_2$ 1.60, $MgSO_4$ 1.20, $NaHCO_3$ 24.90, KH_2PO_2 1.20, and glucose 11.10.

The following drugs were used: ethyl alcohol (Merck), verapamil (Knoll), sodium nitrite, papaverine (Sigma) and hydralazine (Ciba-Geigy). A solution of each antagonist was prepared with distilled watar. All doses of the drugs were calculated in terms of the base weight. The results were expressed as means ± SEM. Significance of differences was calculated by Student's *t* test[15]. P values less than 0.05 were considered to be significant.

Results

Ethyl alcohol caused concentration dependent contraction of the isolated human umbilical artery. A 2000 mg/dl concentration of ethyl alcohol produced maximum contraction which was 64.8 ± 3.08% of 80 mM KCl-induced response (Fig. 1).

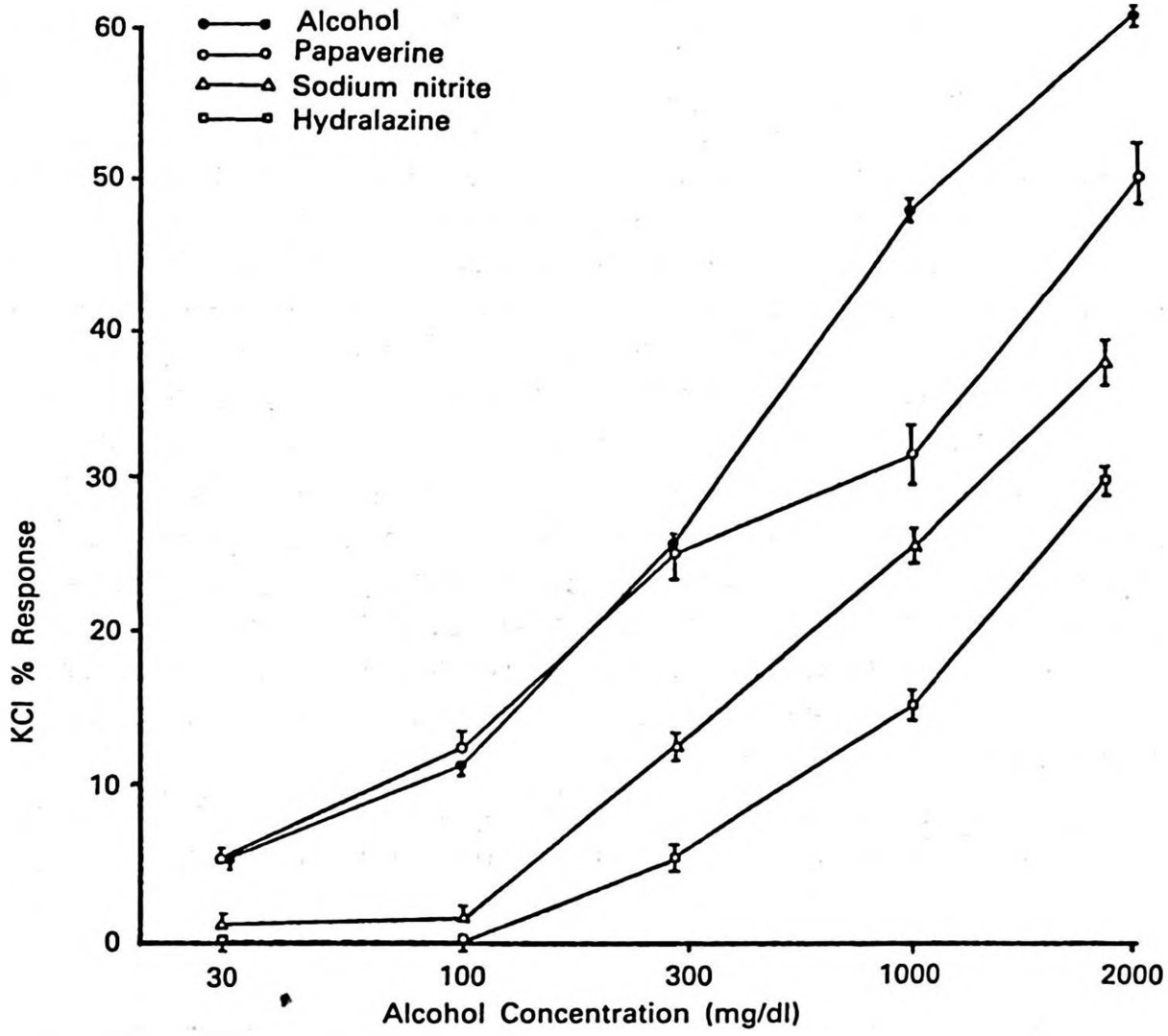

Fig. 1: Contractions produced by ethyl alcohol in the human umbilical artery and antagonistic potency of some vasodilator agents.

When 10^{-6}M verapamil was added to the bath, maximum contraction induced by ethyl alcohol and the control EC_{50} value did not change significantly. On the other hand, the same concentration of papaverine, sodium nitrite and hydralazine reduced the maximum response to alcohol and increased the control EC_{50} values significantly ($p < 0.05$; Table I).

TABLE I: The EC_{50} Value of Some Vasodilator Agents

	Control	10^{-6} M Antagonist	n
Verapamil	720 ± 3.24	700 ± 5.38	19
Papaverine	700 ± 9.68	1000 ± 9.51*	11
Sodium nitrite	380 ± 2.58	1200 ± 9.19*	13
Hydralazine	400 ± 4.54	1900 ± 9.41*	12

* Significantly higher than the control ($p < 0.05$)

Discussion

In this study ethyl alcohol produced dose-dependent contractions of the isolated human umbilical artery. This effect had previously been shown by Alture et al[7]. In his study, various receptor antagonists such as phentolamine, methysergide, pyrilamine, metiamide, atropine and propranolol were used in order to inhibit the contractile, response, however, these drugs were determined to be ineffective. Moreover, indomethacin, a prostaglandin synthesis inhibitor was proved to be ineffective. According to these findings, authors have claimed that activation of these receptors and also prostaglandin synthesis do not play a role in ethyl alcohol-induced contractions.

In the present experiment, smooth muscle relaxants such as papaverine[16], sodium nitrite and hydralazine[17] have inhibited the contractions produced by ethyl alcohol, although verapamil[18], a calcium channel-blocker, has been observed to be ineffective. The ineffectiveness of verapamil has shown that alcohol-induced contractions of the human umbilical artery is not mainly dependent on extracellular Ca^{++}, and that probably an intracellular mechanism may play a role in this response.

In conclusion, smooth muscle relaxing drugs may be effective in eliminating an alcohol-induced vasospastic effect in the human umbilical artery.

Summary

In this in vitro study, the vasodilator effects of certain drugs such as verapamil, papaverine, sodium nitrite and hydralazine on ethyl alcohol-induced contractions were investigated in the isolated human umbilical artery. Ethyl alcohol caused dose dependent contractions in this tissue. Papaverine, sodium nitrite and hydralazine were found to be effective.

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