INFLUENCE OF POTASSIUM CHLORIDE ON ALCOHOL ABSORPTION

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Simultaneous intragastric administration of large doses of KCl (430 mg/kg and 860 mg/kg) with ethanol (4 g/kg) significantly reduces blood alcohol levels and diminishes manifestations of alcohol intoxication in rats. It was shown with parenteral administration of alcohol that the effect is not related to an acceleration of alcohol metabolism. Analysis of alcohol concentrations of gastric and intestinal content as well as in situ studies with animals whose stomachs were ligated at the pylorus revealed that KCl interferes with the absorption of alcohol through inhibition of gastric absorption and gastric emptying. The finding that equimolar concentrations of NaCl were unable to duplicate the described effects characterizes them as specific actions of the potassium ion.

The findings by Israel et al. (1) that ethanol inhibits the NaMg activated membrane ATPase of brain tissue with consequent reduction of potassium gradients across cell membranes lead us to study the influence of large oral and parenteral doses of potassium salts on manifestations of acute alcohol toxicity. During the conduct of this study it was noticed that KCl when administered orally together with alcohol decreased the level of alcohol intoxication in rats; however, the effect was not related to the restoration of higher intracellular potassium levels but rather to an inhibitory influence of KCl on the absorption of alcohol from the gastrointestinal tract.

Data of blood alcohol levels, analysis of gastric and intestinal contents as well as studies of alcohol absorption from the ligated stomach will be reported which suggest that KCl not only interferes with gastric emptying but also inhibits the absorption of alcohol from the stomach.
Materials and Methods

Female ASR Sprague-Dawley rats were used for the experiments. Because weights of the animals in the colony varied from 150g to 400g, each experimental group was compared with its own control group which matched it closely in weight and numbers. Alcohol was administered either through a stomach tube intragastrically in dosage of 4 g/kg using a 25% V/V solution of ethanol in physiological saline or intravenously in dosage of 2 g/kg using a 10% V/V solution in saline. Potassium chloride was added to the intragastrically administered alcohol solutions in quantities to provide dosages of 215 mg/kg, 430 mg/kg and 860 mg/kg without altering total fluid volume of the alcohol saline solution administered per kg of body weight. In one study KCl was administered intraperitoneally while alcohol was given by the intragastric route. The animals were deprived of food 12 hours before start of the experiment if not indicated otherwise.

Animals used for experiments studying the absorption of alcohol from the ligated stomach were anesthetized with ethanol-free ether. The duodenum was isolated through a small incision in the right epigastrium, the pyloric region ligated with a suture and the wound closed with wire clips. Accumulation of secretions in the ligated stomach, which can lead to aspiration, influenced us not to extend the experiments beyond the first 1½ hour period following the administration of alcohol. In those studies where the fractions of unabsorbed alcohol in stomach and small intestine were measured, animals were sacrificed at specified time intervals after alcohol administration. Stomach contents were secured by ligation of the esophagus and pylorus, intestinal contents by ligation of the terminal ileum at the cecal border. The organs were then removed from the animal and their contents collected in measuring cylinders. The stomach was rinsed with 5 ml saline, the intestinal tract flushed with 10 ml saline, assuring removal of as much fluid as possible by squeezing motions.

Plasma potassium levels were determined by flame photometry.
Alcohol Determinations

Alcohol determinations were performed on blood plasma, gastric and intestinal content. Blood was collected at specified time intervals from the tail and aspirated in heparinized microhematocrit capillary tubes. These were centrifuged, broken at the plasma-red cell border and the plasma transferred to micropipettes or microsyringes for analysis with the alcohol dehydrogenase or gas chromatographic method, respectively. The enzymatic determination was conducted according to Bücher and Redetzki (2,3). The gas chromatographic assay utilized a chromasorb W-30% carbowax column with flame ionization detector. Column temperature was set at 100°C, injection port at 110°C and the detector at 125°C. Blood plasma or supernatants of the centrifuged stomach and intestinal tract contents were injected directly into the column. Ethanol standards were prepared according to the procedure described by Redetzki (4).

Results

Analysis of Blood Alcohol Levels After Simultaneous Intragastric Administration of Alcohol and Potassium Chloride and Alcohol and Sodium Chloride Respectively.

A total of 72 rats were used for these experiments. The alcohol dose (4 g/kg) was equal for all animals. Three dose levels of KCl were analyzed. The lowest dose (215 mg/kg) did not alter blood alcohol concentrations when the experimental group was compared with the controls (Fig. 1). However, animals which received the intermediate (430 mg/kg) and highest dose (860 mg/kg) had significantly lower blood alcohol levels. While most of the control animals lost their righting reflex and appeared to be severely intoxicated, those in the latter two experimental groups remained reactive throughout the period of observation and exhibited only moderate levels of ataxia and incoordination. The reduction in the rate of rise of blood alcohol levels was already maximal at the 430 mg/kg dose level and could not significantly be intensified with the higher dose. Blood alcohol values were on the average 28% and 29% respectively below those of the controls when measured at the time of absorption peaks. It was also not
Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 215 mg/kg KCl. Nine animals in each group. Fasting period 12 hours. Bars: S.E.M.

![FIG. 1](image)

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Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 215 mg/kg KCl. Nine animals in each group. Fasting period 12 hours. Bars: S.E.M.

Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 430 mg/kg KCl. Nine animals in each group, non-fasted.

![FIG. 2](image)

FIG. 2
Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 430 mg/kg KCl. Nine animals in each group, non-fasted.

influenced by the presence or absence of food in the stomach. Figure 2 shows the effect of the intermediate dose on animals which had access to food up to the start of the experiment. Figure 3 depicts data from an experiment with the high KCl dose using animals which have been fasted for 24 hours. The only significant difference between the two groups is that the blood alcohol plateau (absorption peak) was reached after 3 hours in the former and 1½ hours in the latter. The reduction in blood levels caused by KCl is evident in both experiments. Even the high KCl dose was well tolerated. Intermittent EKG recordings
from three randomly selected animals failed to reveal any change in heart rate, cardiac irregularities or arrhythmias.

Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 860 mg/kg KCl. Nine animals in each group. Fasting period 24 hours.

To evaluate the significance of the KCl effect and to obtain data on its mechanisms of action, identical experiments were carried out with NaCl in equimolar concentrations. Figure 4 shows the results of an experiment in which 337 mg/kg NaCl were administered together with alcohol. This dose corresponds osmotically with the intermediate dose of KCl which effectively reduced blood alcohol levels in previous experiments. There were no differences between the NaCl and control group.

Investigation of a Possible Influence of Potassium Chloride on Alcohol Metabolism. To study possible effects of KCl on the rate of disappearance of alcohol from the blood, experiments were conducted in which either a KCl solution (430 mg/kg) or physiological saline was administered intragastrically. Thirty minutes later 2 g/kg alcohol was given intravenously. Figure 5 shows that there was no difference in the average rate of decline of blood alcohol values between the KCl pretreated and control animals when followed for a period of 7 hours. The average β₆₀ (rate of decline of blood alcohol level per hour) of experi-
mental and control groups was 23.6 mg% and 24.0 mg% respectively.

**FIG. 4**

Blood alcohol levels after simultaneous intragastric administration of 4 g/kg ethanol and 337 mg/kg NaCl. Nine animals in each group.

**Study of the Influence of Potassium Chloride on Alcohol Absorption from Stomach and Small Intestine.** Twenty-two animals each were used in experimental and control groups. While 4 g/kg of alcohol were administered to both groups, the

**FIG. 5**

Blood alcohol after intragastric administration of 430 mg/kg KCl followed 30 minutes later by 2 g/kg ethanol iv. Controls: saline plus alcohol. Three animals in each group.

former received simultaneously 430 mg/kg KCl, the latter physiological saline in equal fluid volume. After ½, 1½ and 3 hours, 6, 12 and 3 animals respec-
tively were sacrificed from each group and their blood alcohol and the amount of alcohol that remained in stomach and intestinal tract were analyzed. Figure 6 demonstrates data from these studies. By expressing the amount of alcohol present in stomach and intestinal tract in mg per 100 g of body weight, the results can be better correlated with corresponding blood alcohol values and total body dose of alcohol. It can be seen that the animals which received KCl had significantly lower blood alcohol values. The amount of alcohol remaining in the stomach at any time interval exceeded that of the controls. These differences were statistically significant for the 1½ and 3 hour values. The uniformly low alcohol concentrations in contents of the small intestine reflect the rapid and efficient absorption of alcohol in this region of the intestinal tract. Administration of KCl did not alter this capacity.

![Graph showing blood alcohol levels and alcohol content in stomach and intestines](image)

**FIG. 6**

Blood alcohol levels and gastric and intestinal tract alcohol content after simultaneous administration of 4 g/kg ethanol and 430 mg/kg KCl. Twenty-one animals in each group.

Investigation of Effect of Potassium Chloride on Alcohol Absorption from the Ligated Stomach. After ligation of the pylorus, 4 g/kg alcohol with 430 mg/kg KCl or physiological saline was administered as described before. Seven animals from each group were sacrificed ½ hour and 6 each 1½ hours thereafter. The amount of alcohol retained in the stomach and corresponding blood alcohol
values of these animals are depicted in Fig. 7. The significantly higher stomach alcohol content of the experimental group at 1½ hours demonstrates the inhibitory effect of KCl on gastric absorption of alcohol. While plasma alcohol concentrations of the KCl group stayed below those of the controls these differences were not statistically significant.

Blood alcohol levels and gastric fluid alcohol content after simultaneous intragastric administration of 4 g/kg ethanol and 430 mg/kg KCl. Pylorus ligated. Twenty-one animals in each group.

Study of the Influence of Plasma Potassium Concentration on Alcohol Absorption.

In order to exclude any possible effects of high plasma potassium levels on alcohol absorption from the gastrointestinal tract, blood alcohol concentrations were determined in twelve animals after they had received 4 g/kg alcohol intragastrically followed immediately by an intraperitoneal injection of 430 mg/kg KCl. Eleven control animals were treated identically with the exception that isotonic saline was used instead of KCl. There were no statistically significant differences between the blood alcohol concentrations of the experimental and control group when analyzed ½, 1½, 3, 5 and 7 hours after administration of alcohol. Plasma potassium levels ranged from 3.4 m eq/l to 5.0 m eq/l in the controls and from 5.5 m eq/l to 12.7 m eq/l in the experimental
animals with highest values occurring 30 minutes after injection of KCl. One animal died during the experiment, possibly from the effects of hyperkalemia.

Discussion

Israel et al. (1) in their report that ethanol inhibits the NaK-Mg stimulated ATPase of brain tissue also showed that deliberate elevation of extracellular K⁺ concentration decreases the degree of intoxication produced by a constant dose of alcohol. In their studies on rats, KCl (373 mg/kg) was administered together with ethanol (2 g/kg) intraperitoneally. Measuring levels of intoxication by the inclined-plane test, they observed a small but significant improvement in the KCl treated animals. Blood alcohol levels of these animals however were not significantly different from those of the control group.

Our experiments which showed that simultaneous intragastric administration of alcohol with KCl reduced the rate of rise of blood alcohol levels and decreased CNS manifestations of alcohol intoxication might be explained by two different mechanisms: 1) KCl interferes with the absorption of alcohol, or 2) KCl accelerates the metabolism of alcohol. The second assumption could be excluded since experiments with parenteral administration of alcohol were unable to demonstrate any influence of KCl on the rate of decline of blood alcohol levels. By studying the absorption of alcohol from the ligated stomach and by analyzing alcohol concentrations of gastric and intestinal contents at various time intervals after administration of alcohol, it was possible to confirm the first assumption. Evidence for this mechanism was provided by the findings that KCl increases the retention time of alcohol in the stomach and that it reduces absorption of alcohol from the ligated stomach. For the further elucidation of these effects, it was of great interest to demonstrate that they could not be duplicated by sodium chloride administered in equimolar concentration and dose. Since this eliminated an unspecific osmotic influence, it became necessary to consider more specific effects of potassium salts on the gastrointestinal tract and to relate these to the physiology of alcohol absorp-
Alcohol absorption is influenced by various factors among which the amount of food present in the stomach, the concentration of ingested alcohol and gastric motility and emptying time have received most attention (5,6,7). More recent studies have established the existence of a direct relationship between the rate of alcohol absorption and intestinal blood flow (8).

Potassium salts are local irritants to the gastric mucosa (9,10). Administration of KCl in enteric-coated tablets may be a cause of intestinal ulcers and stricture formation (11,12). Investigations about the erosive qualities of KCl have established that the salt interferes with blood supply of the intestinal mucosa causing venous spasm, stasis and edema (13). Ching-Chung Chou, et al. (14), measuring venous outflow from isolated intestinal loops, provided evidence that aqueous solutions of KCl produced an initial transient rise followed by a progressive fall in blood flow. Since it can be assumed that these findings apply also to the gastric mucosa, a satisfactory explanation for the reduction of gastric alcohol absorption is provided. Concerning the absorption of alcohol from the small intestine, the lack of difference in alcohol content as well as the fact that alcohol concentrations in this segment remained very low throughout the absorption phase indicates that any inhibitory effects of KCl are apparently compensated by the large mucosal surface area which greatly facilitates absorption. The experiment in which alcohol was administered intragastrically and KCl by intraperitoneal injection showed clearly that the actions of the potassium ion are of a local rather than systemic nature.

Since the high efficiency of intestinal alcohol absorption was confirmed by our findings that the amount of alcohol detectable in the small intestine at any time during the absorption phase was negligible, it became evident that an inhibitory effect of KCl on gastric emptying would significantly decrease its rate of absorption. The observation that rats which received KCl together with alcohol retained larger amounts of alcohol in their stomach at ½, 1½ and
3 hours after administration confirms this assumption. The average gastric fluid volume of animals receiving alcohol with KCl was 18%, 3% and 40% larger than that of the controls when studied ¼, ½ and 3 hours after alcohol adminstration; however, these differences were not statistically significant. The importance of gastric emptying is further emphasized by the fact that blood alcohol concentrations of the animals with duodenal ligation were significantly below those of unligated rats studied ¼ and ½ hours after instillation of alcohol.

In view of the findings by Shay et al. (15) consideration was given to the possibility that duodenal ligation might lead to gastric mucosal damage with ulcer formation. Many differences between our and Shay's experimental design made it unlikely that such effects would occur. The latter author stresses the importance of a prolonged fasting period (48-72 hours) for the development of ulcers. He also found that at least 4 hours of duodenal ligation were needed in order to produce ulcers in a significant number of animals. In contrast our animals were fasted for 12 hours only and the time with duodenal ligation was restricted to ½ hours. The instillation of fluid into the stomach - we used a total volume of 2.03 ml/100g of rat - would also serve to prevent any effects of concentrated gastric juice on the mucosa. Finally it is known that in contrast to alcohol concentrations below 8.2% which stimulate gastric acid secretion (16), higher concentrations of the order used in our experiments have inhibitory effects (17). Examination of the gastric mucosa of the animals with duodenal ligation through a dissecting microscope (magnification up to 30x) revealed a few scattered areas of mucosal punctate bleeding; however, there was no additional evidence of mucosal damage or ulcer formation.

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References


