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The Role of the Gastric and Hepatic Vagus in Voluntary Alcohol Intake

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TOTH, P., M. A. LINSEMAN, E. PERLANSKI AND L. A. GRUPP. *The role of the gastric and hepatic vagus in voluntary alcohol intake*. PHARMACOL BIOCHEM BEHAV **36**(1) 69–76, 1990.—The present study investigated a possible role for neural signals sent from the liver and stomach to the brain in the regulation of alcohol intake. Experiment 1 showed that gastric vagotomy (GVX) reduced the intake of 3% alcohol and 6% alcohol, while water intake was increased. This effect was not due to an alteration in pharmacokinetics, although an alteration in taste function could not be ruled out. Angiotensin II reduced the intake of 6% alcohol and stimulated the intake of water similarly in both GVX and sham groups. In Experiment 2 rats were subjected to hepatic vagotomy or sham laparotomy and then offered a choice between an alcohol solution and tap water for 40 min each day. Although hepatic vagotomy (HVX) did not alter the intake of 3% alcohol or water, 6% alcohol intake was significantly reduced. Angiotensin II decreased 6% alcohol intake and increased water intake similarly in both groups. These experiments indicated that interrupting information from the liver and stomach to the brain by selective gastric and hepatic vagotomy can decrease voluntary alcohol intake. Since vagal afferent nerves are thought to participate in the control of food intake, the present findings support the hypothesis that the "food-like" qualities of alcohol, i.e., calories and taste, can contribute to the regulation of alcohol intake.

Ethanol intake Vagotomy Hepatic vagus Gastric vagus Food intake

ASIDE from its action on the brain, alcohol shares certain properties with food. It is consumed orally, has an acceptable taste at low concentrations and contains calories (22,25). Therefore, alcohol consumption can be viewed not only as the intake of a *drug* but also of a *calorically rich foodstuff* (9,25). These considerations which predict that alcohol intake might be influenced by its food qualities finds support in the fact that agents and manipulations known to alter feeding behavior also modify alcohol intake. For example, the putative satiety peptide CCK-8 and serotonin uptake inhibitors, both known to reduce food intake, also reduce alcohol intake (4,9). There may be a commonality between mechanisms involved in the regulation of feeding and of alcohol intake.

In recent years, renewed emphasis has been placed on the role of the periphery in the control of food intake (20). The hypothalamus was once thought to be the sole regulatory center of food intake (29), however it is now recognized that signals from the periphery also contribute to the control of food intake (20). The subdiaphragmatic vagus nerve is one of the sites thought to be responsible for the peripheral control of consummatory behavior (20). Since 80–90% of the fibres contained in the vagus are afferent, the vagus is thought to carry a great deal of sensory information from the viscera to the brain (1). This neural information is likely to contribute to the regulation of food intake since vagotomy is known to alter feeding behavior (8,18).

Although a great deal of evidence suggests that neural information from the abdominal organs to the brain is important in the regulation of food intake, it is unknown to what extent signals from these organs also influence ethanol intake. Therefore, the purpose of the following experiments was to determine the role, if any, of the information originating from the liver and stomach and reaching the brain has in the regulation of ethanol intake. This was examined by assessing the effect of hepatic or gastric vagotomy on voluntary ethanol intake because the vagus carries visceral afferent information to the brain (1), and total subdiaphragmatic vagotomy has recently been shown to reduce ethanol intake (10). Additionally, the effects of peripherally administered angiotensin II (ANG II) on voluntary alcohol intake were assessed in order to investigate their interaction with selective vagotomy on alcohol intake. This peptide was chosen because it modifies alcohol intake (5) and because gastric vagotomy has already been shown to block some of the effects of ANG II (6).

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EXPERIMENT 1

This experiment examined the effect of gastric vagotomy (GVX) on voluntary alcohol intake under conditions of limited access to alcohol. The first part of the experiment assessed the effect of GVX on alcohol intake, on the ability of ANG II to reduce alcohol intake and on the distribution and metabolism of alcohol. The second part of the experiment examined the effect of GVX on the rate of alcohol absorption and on taste function.

METHOD

Subjects

The subjects were 89 naive male Wistar rats (Charles River, Montreal, Canada) weighing 200–350 g. Animals were individually housed and maintained on a reverse 12-hr/12-hr light/dark cycle with lights off at 7 a.m. Ad lib access to food, water and mash (one part powdered Purina Rat Chow to three parts tap water) was provided in home cages throughout the experiment. Mash was provided to prevent gastric retention of solid food which can occur after GVX as a consequence of decreased gastric motility and acid secretion (16).

Surgery

Rats underwent GVX (n = 57) or sham laparotomy (n = 32) according to the method outlined by Smith and Jerome (28) (GVX can sever fibres of the coeliac branch of the vagus nerve) (3). Animals were anesthetized with sodium pentobarbital (55 mg/kg; Somnotol, M.T.C. Pharmaceuticals) administered by the intraperitoneal (IP) route. A 5-cm incision was made through the skin and abdominal muscles to expose the upper abdominal organs. Exposure of the lower portion of the esophagus was achieved by displacing the liver to the right with moist gauze and gently pulling the stomach out of the peritoneal cavity with a 3-0 stay suture placed along the greater curvature of the stomach. An Olympic microscope (3.1–20×) was used to locate the anterior (right) and posterior (left) vagal trunks. The anterior gastric branch is the continuation of the anterior trunk below the hepatic and accessory coeliac branches. The posterior vagal trunk divides into the gastric and coeliac branches within the fatty mesentery to the left of the esophagogastric junction. After the anterior and posterior gastric branches were identified, each was ligated with two 5-0 silk sutures and the segment of the nerve between these sutures was removed. The gauze sponges and gastric stay suture were then removed, and the stomach and liver were replaced into their normal position. The muscle and skin layers were closed with interrupted sutures of 3-0 silk. Following surgery, rats were given 0.1 ml of penicillin (Penlong XL, Rogar/STB) administered by the intramuscular route, then placed under a heat lamp until they recovered from anaesthesia and finally were returned to their home cages. Animals were allowed 6–28 days to recover postoperatively. Sham laparotomy consisted of the same operative procedure, except the gastric vagal branches were not ligated or cut.

Verification of Surgery

Part 1. At the conclusion of the experiment, completeness of GVX was verified in animals (GVX: n = 37, sham: n = 22) of the experiment by measuring stomach weight 12 hr after food-deprivation (16). Gastric retention of solid food occurred after GVX due to decreased gastric motility and acid secretion and resulted in a stomach to total body weight ratio >0.020 (16). This criterion was used to verify completeness of GVX. Rats were weighed and then deprived of food for 12 hr commencing at 10 p.m. and an overdose of sodium pentobarbital was administered to animals the next morning. The stomach was ligated at the esophagus and duodenum, and then removed and weighed.

Postfast stomach to total body weight determination verified GVX in 25 of 37 animals. The data for the animals not judged to have complete GVX are not presented.

Part 2. Completeness of GVX in animals of the second part of the experiment (GVX: n = 20, sham: n = 10) was verified by either the postfast stomach to total body weight ratio or by employing a neutral red dye to determine basal gastric acid secretion according to the method of Legros and Griffith (12). A lack of basal gastric acid secretion was reflected by an absence of neutral red dye secretion by the gastric mucosa. This resulted from deinnervation of efferent gastric vagal fibres and was taken to verify completeness of GVX. At the conclusion of the experiment, rats were anesthetized with IP sodium pentobarbital (55 mg/kg). The femoral vein was cannulated and then the abdomen was opened with a mid-line incision. After the stomach was isolated and exteriorized, the abdomen was closed as much as possible without constricting the esophagus. A careful incision was made along the greater curvature of the stomach and stomach contents were removed using 0.9% saline. The weight of these stomach contents was used as an approximation of stomach weight. The stomach was then pinned out flat onto a wooden board and Whatman's No. 1 filter paper was cut into pieces that fitted onto the pinned out stomach. The pieces were soaked in warm 0.9% saline and placed onto the stomach so that no air bubbles were present between the filter paper and the mucosa. A volume of 0.8 ml of neutral red dye was injected into the femoral vein. The filter paper was replaced 10 and 20 min after injection. Animals were sacrificed at the conclusion of the neutral dye test.

Four of 20 gastric vagotomized animals were judged not to have complete GVX by either the dye staining technique or the stomach contents weight determination. The data obtained from these animals are not reported. Additionally, one sham animal died during the taste tests and its data were not included in the analysis of the taste tests.

In agreement with previous findings (8), GVX tended to reduce body weight compared to sham-operated animals (approximately 20 g).

Procedure

Part 1. A limited access drinking procedure was used to promote alcohol consumption (13,15). Each day during the dark cycle, rats were weighed and then transferred to "drinking cages" where an alcohol solution was available in one graduated tube and tap water in another. The position of these tubes was alternated daily and no food was available in the drinking cage. After 40 min had elapsed, animals were returned to their home cages and alcohol and water consumption were measured to the nearest 0.1 ml.

For 10–12 days the alcohol concentration was 3% w/v and was then increased to 6% w/v for the next 10–12 days. Following this, half of the animals (GVX: n = 13, sham: n = 12) were maintained on the limited access procedure for 7 more days and received 400 μg/kg ANG II (arginine-1-valine-5 angiotensin II, Hypertensin) administered by the subcutaneous (SC) route immediately before the 40-min access period to 6% alcohol and water. After this, the effect of GVX on alcohol distribution and elimination was examined in these same animals. A 2.5 g/kg IP dose of alcohol was administered and then blood alcohol levels were measured (11) from the tail vein samples obtained at time = 0.5, 1, 1.5, 2, 2.5, 3, 4, 5 and 6 hr after alcohol administration.

Part 2. In order to determine whether GVX could alter the relationship between amount of alcohol consumed and the result-

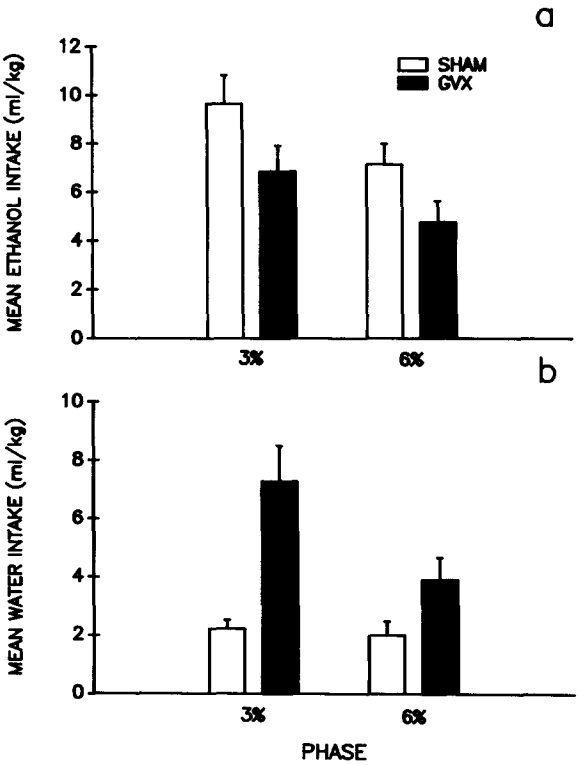

FIG. 1. (a) Mean ethanol intake (ml/kg) for the gastric-vagotomized and sham-operated control groups across the 3% ethanol and 6% ethanol phases of Experiment 1. Ten ml/kg of 3% ethanol is equivalent to an ethanol dose of 300 mg/kg and 10 ml/kg of 6% ethanol is equivalent to an ethanol dose of 600 mg/kg. (b) Mean water intake (ml/kg) for the gastric-vagotomized and sham-operated control groups across the 3% ethanol and 6% ethanol phases of Experiment 1. Vertical lines represent the standard error of the mean.

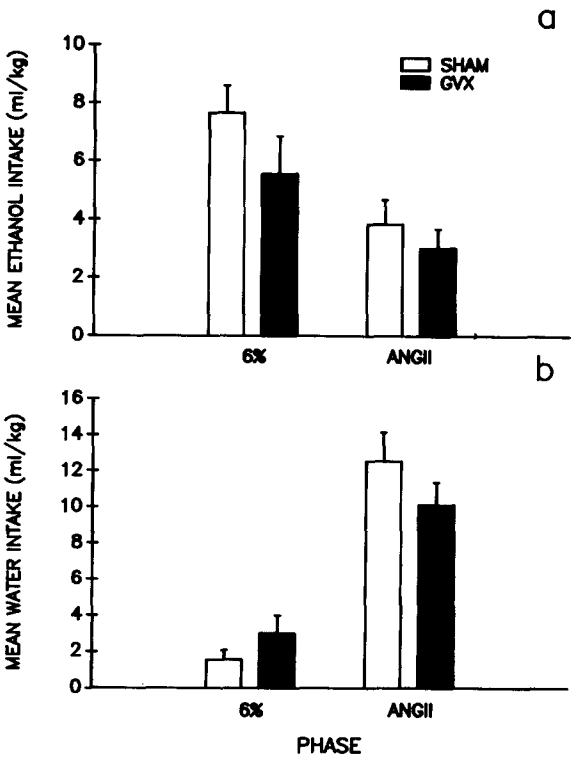

FIG. 2. (a) Mean 6% ethanol intake (ml/kg) for the gastric-vagotomized and sham-operated control groups of Experiment 1 before (6%) and during (ANG II) treatment with 400 μg/kg angiotensin II. Ten ml/kg of 6% ethanol is equivalent to an ethanol dose of 600 mg/kg. (b) Mean water intake (ml/kg) for the gastric-vagotomized and sham-operated control groups of Experiment 1 before (6%) and during (ANG II) treatment with 400 μg/kg angiotensin II. Vertical lines represent the standard error of the mean.

ant blood alcohol levels achieved, blood alcohol levels were measured after a single drinking session in animals from the second part of the experiment. Animals were offered a choice between 6% alcohol and water for 20 min, after which blood samples were obtained.

In order to determine whether GVX altered the rate of alcohol absorption, animals received 1 g/kg of alcohol administered by gavage and blood alcohol levels were measured from tail vein blood samples obtained at time = 5, 10, 15, 20, 25, 30, 45 and 60 min after alcohol administration.

Finally, the effect of GVX on taste function was assessed. A flavored solution replaced alcohol in the limited access procedure. Animals were offered a choice between water and a noncaloric sweet tasting solution containing 0.2% saccharin for 40 min each day for 5 days. The saccharin solution was then replaced first with a salty tasting solution containing 0.1 M saline for 5 days and then with a calorically rich sweet tasting solution containing 20% sucrose for a final 5 days.

RESULTS

Figure 1a shows mean alcohol intake for the GVX and sham groups during the 3% and 6% alcohol phases. A two-way analysis of variance with Group as the between subjects factor and Phase as the within subjects factor revealed a significant effect of Group, $F(1,45) = 3.96$, $p = 0.05$, and Phase, $F(1,45) = 15.66$, $p < 0.001$, but a nonsignificant Group × Phase interaction, $F(1,45) = 0.14$, NS, indicating that GVX significantly reduced alcohol intake and all animals drank significantly less of the 6% alcohol solution. Post hoc analyses showed that GVX reduced alcohol intake during both the 3% alcohol, $t(44) = 1.76$, $p < 0.05$, and 6% alcohol, $t(44) = 1.92$, $p < 0.05$, phases. These results indicate that GVX significantly decreases alcohol intake.

Figure 1b illustrates the mean water intake for the GVX and sham groups during the 3% and 6% alcohol phases. A two-way analysis of variance yielded a significant effect of Group, $F(1,45) = 11.32$, $p = 0.001$, and Phase, $F(1,45) = 12.53$, $p = 0.001$, and a significant Group × Phase interaction, $F(1,45) = 9.57$, $p < 0.005$. This indicates that GVX significantly enhanced water intake, that water intake significantly varied with the concentration of alcohol offered and that differences among the groups depended on the alcohol concentration offered. Post hoc analysis of the Group effect revealed that GVX increased water intake during both the 3%, $t(44) = 3.8$, $p < 0.001$, and 6% alcohol, $t(44) = 2.02$, $p < 0.05$, phases.

Figure 2a shows mean alcohol intake for the GVX and sham groups during the same 6% alcohol and ANG II administration phases. A two-way analysis of variance yielded a nonsignificant effect of Group, $F(1,23) = 1.44$, NS, a significant effect of Phase, $F(1,23) = 23.74$, $p < 0.001$, and a nonsignificant Group × Phase interaction, $F(1,23) = 0.97$, NS, indicating that ANG II significantly reduced alcohol intake and that the GVX and sham groups did not significantly differ in their response to ANG II. Alcohol

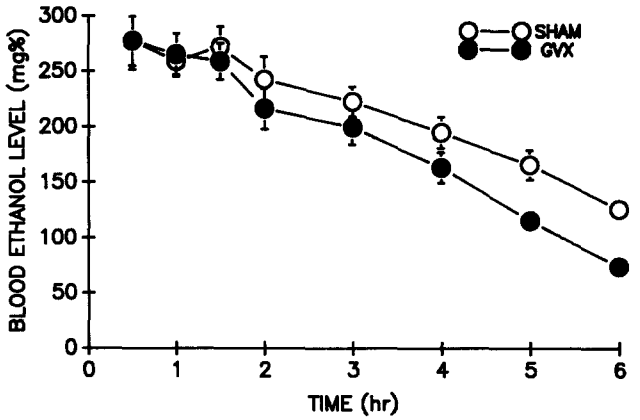

FIG. 3. Mean blood ethanol levels (mg %) for the gastric-vagotomized and sham-operated control groups measured at various times after an initial dose of 2.5 g/kg ethanol administered IP at time zero. Vertical lines represent the standard error of the mean.

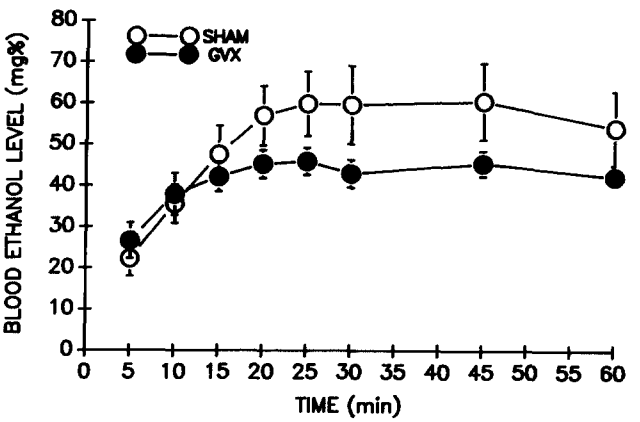

FIG. 4. Mean blood ethanol levels (mg %) for the gastric-vagotomized and sham-operated control groups measured at various times after an initial dose of 1 g/kg ethanol by gavage at time zero. Vertical lines represent the standard error of the mean.

intake was reduced by ANG II in both the GVX, $t(12) = 3.10$, $p<0.01$, and sham, $t(11) = 4.16$, $p<0.005$, groups. These results indicate that GVX does not alter the ability of ANG II to reduce alcohol intake.

Figure 2b gives the mean water intake for the GVX and sham groups during the 6% alcohol and ANG II administration phases. A two way analysis of variance yielded a nonsignificant effect of Group, $F(1,23) = 0.17$, NS, a significant effect of Phase, $F(1,23) = 62.94$, $p<0.001$, and a nonsignificant Group × Phase interaction, $F(1,23) = 2.83$, NS, indicating that ANG II significantly increased water intake and that the GVX and sham groups did not significantly differ in their response to ANG II. Post hoc tests showed that water intake was increased in both the GVX, $t(12) = -4.38$, $p<0.005$, and sham, $t(11) = -6.93$, $p<0.005$, groups. These findings indicate that the effect of ANG II on water intake is not altered by GVX. This latter finding is unlike that of Jerome and Smith (6) who found that GVX attenuates water intake to systemically injected ANG II. However, in the present experiment the animals were tested in the dark cycle when they are most active and 6% alcohol was concurrently available and consumed along with the water. These differences in procedure may account for the discrepancy in results.

Figure 3 gives the blood alcohol levels over a 6-hr period after 2.5 g/kg of ethanol (IP) in the GVX and sham groups. The data for one GVX and two sham animals were discarded due to unanalyzable samples. Volume of distribution of alcohol was determined for each animal by dividing ethanol dose, i.e., 2.5 g/kg, by the initial blood alcohol concentration, computed by extrapolating the alcohol distribution curve to time = 0. Statistical analysis revealed no difference between the volumes of distribution of alcohol in the GVX and sham groups, $t(18) = 0.01$, NS. The rate of alcohol metabolism was determined from the slope of the descending portion of the alcohol distribution curve. Statistical analysis also revealed that alcohol metabolism was increased in the GVX group as compared to the sham group, $t(18) = 4.32$, $p<0.001$.

Figure 4 gives blood alcohol levels for the GVX and sham groups over a 1-hr period after 1 g/kg of alcohol by gavage. The data for one gastric-vagotomized and two sham animals were eliminated because of unanalyzable samples. The rate of alcohol absorption was determined for each animal by calculating the slope of the line of best fit between blood alcohol levels at time = 5, 10, 15 and 20 min after alcohol administration and found to be lower in the GVX group, $t(20) = 2.33$, $p<0.05$. These findings indicate that GVX slowed the rate of alcohol absorption and, consequently, lower blood alcohol levels at any given time were seen in the GVX group. Although GVX increased the rate of alcohol metabolism and reduced the rate of alcohol absorption, it is unlikely that these differences in alcohol pharmacokinetics can account for the reduced alcohol intake in the GVX group since animals tend to titrate their alcohol consumption against blood

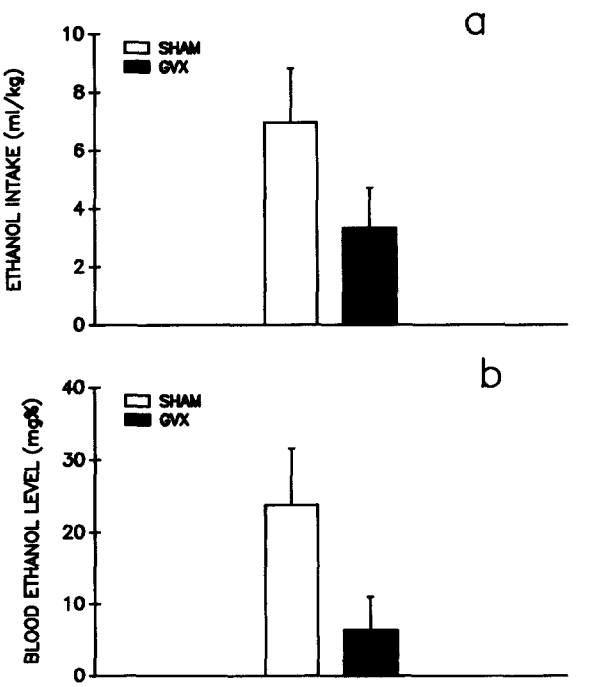

FIG. 5. (a) Mean 6% ethanol intake (ml/kg) for the gastric-vagotomized and sham-operated control groups during a single 20-min drinking session. Ten ml/kg of 6% ethanol is equivalent to an ethanol dose of 600 mg/kg. (b) Mean blood ethanol levels (mg %) for the gastric-vagotomized and sham-operated control groups immediately after a single 20-min drinking session. Vertical lines represent the standard error of the mean.

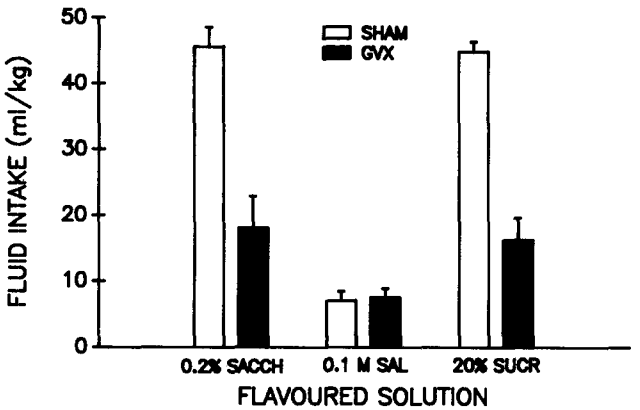

FIG. 6. Mean fluid intake of flavoured solutions (ml/kg) for the gastric-vagotomized and sham-operated control groups across the three flavoured solutions offered. SACH = saccharin, SAL = saline, SUCR = sucrose. Vertical lines represent the standard error of the mean.

alcohol levels (14) and lower blood alcohol levels would therefore tend to promote greater not lesser alcohol intake.

Figure 5 shows the mean alcohol intake (panel a) and blood alcohol level (panel b) after a single 20-min drinking session in the GVX and sham groups. The GVX group consumed less alcohol than the sham group, $t(23) = 1.60$, $p<0.05$, and achieved lower blood alcohol levels, $t(23) = 2.04$, $p<0.05$, immediately after the drinking session. These findings indicate that blood alcohol levels in the GVX and sham groups reflect the differences in amount consumed confirming that pharmacokinetic changes were not responsible for the reduction of alcohol intake by GVX.

Figure 6 shows the consumption of 0.2% saccharin, 0.1 M saline and 20% sucrose solutions by the GVX and sham groups. A two-way analysis of variance yielded a significant effect of Group, $F(1,23) = 26.50$, $p<0.001$, and Solution, $F(2,46) = 45.02$, $p<0.001$, and a significant Group × Solution interaction, $F(2,46) = 16.11$, $p<0.001$. This indicates that GVX significantly altered the amount of flavored solutions consumed, that the amount of the flavored solution consumed varied significantly with the particular solution presented and that differences among the GVX and sham groups depended on the flavored solution presented. Post hoc analysis revealed that the GVX group consumed less 20% sucrose, $t(22) = 6.15$, $p<0.001$, and 0.2% saccharin, $t(22) = 4.03$, $p<0.001$, but did not differ from the sham group in its intake of 0.1 M saline, $t(22) = 0.23$, NS. In agreement with previous findings, GVX reduced the intake of sweet solutions (23). On the other hand, the intake of a salty solution was not different in the GVX and sham groups indicating that GVX does not indiscriminately affect the intake of all flavored solutions.

In summary, GVX reduced voluntary alcohol intake and this effect was probably not due to changes in alcohol absorption, distribution or metabolism. Since GVX altered the preference for certain flavored solutions but not others, the reduction in alcohol intake may be a reflection of an alteration in taste function. The ability of ANG II to reduce alcohol intake is not dependent on an intact vagus since ANG II was able to reduce alcohol intake in animals subjected to GVX.

EXPERIMENT 2

This experiment examined the effect of hepatic vagotomy (HVX) on voluntary alcohol intake under conditions of limited

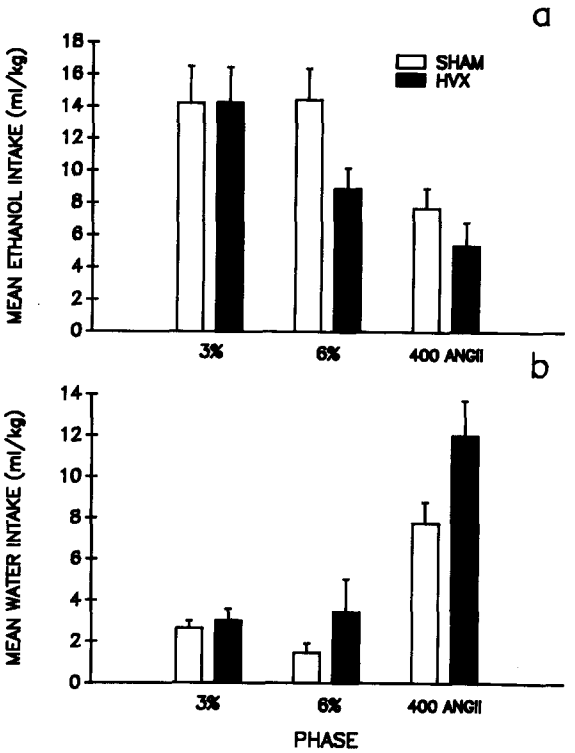

FIG. 7. (a) Mean ethanol intake (ml/kg) for the hepatic-vagotomized and sham-operated control groups across the three phases of Experiment 2. Ten ml/kg of 3% ethanol is equivalent to an ethanol dose of 300 mg/kg and 10 ml/kg of 6% ethanol is equivalent to an ethanol dose of 600 mg/kg. (b) Mean water intake (ml/kg) for the hepatic-vagotomized and sham-operated control groups across the three phases of Experiment 2. Vertical lines represent the standard error of the mean.

access to alcohol. The effect of ANG II on alcohol intake in animals with sham and hepatic vagotomies was also assessed.

METHOD

Subjects

The subjects were 30 naive male Wistar rats (Charles River, Montreal, Canada) weighing 250–350 g. Animals were individually housed and maintained on a reverse 12-hr/12-hr light/dark cycle with lights off at 7 a.m. Ad lib access to food and water was available in home cages.

Surgery

The method used to perform hepatic vagotomy (n = 18) and sham laparotomy (n = 12) was the same as in Experiment 1, except that the hepatic branch and not gastric branches of the vagus was sutured and cut. The hepatic vagus was identified as the first branch of the anterior truck, below the diaphragm, which curves towards the liver. This branch was then isolated from its accompanying blood vessels. Two 5-0 sutures were tied to the hepatic vagus about 5–10 mm apart and the segment between the sutures was removed. Animals were allowed 12–23 days to recover postoperatively.

Verification of Surgery

Histological examination of the surgical tissue removed during surgery was used to verify completeness of HVX. Immediately after sectioning the hepatic vagus, the tissue segment was placed

into a vial containing 5 ml of Modified Bouin's solution. Two days later, the Bouin's solution was replaced with 70% ethanol in distilled water. The tissue was wrapped in onion paper, processed through a tissue processor, embedded in paraffin wax, sectioned, transferred onto standard glass slides and then stained with hematoxylin and eosin. Neural material in the sample was taken to indicate that the hepatic vagus had been removed during surgery.

Histological examination of the surgical material removed during HVX did identify neural tissue in 9 of the 18 samples. Only the data from these 9 animals are reported.

In agreement with previous work (8) HVX did not alter body weight.

Procedure

For 10 days animals were offered a choice between 3% alcohol and water using the limited access procedure. This was followed by 8 days during which animals were offered a choice between 6% alcohol and water. During the final phase of this experiment, which lasted 7 days, the sham and HVX groups both received 400 μg/kg ANG II SC administered immediately prior to the 40-min access period to 6% alcohol and water.

RESULTS

Figure 7a shows the mean alcohol intake of the HVX and sham groups during the 3% alcohol, 6% alcohol and ANG II phases of the experiment. A two-way analysis of variance with Group as the between subjects variable and Phase (3% alcohol and 6% alcohol) as the within subjects variable revealed a nonsignificant effect of Group, $F(1,19) = 1.07$, NS, a significant effect of Phase, $F(1,19) = 4.33$, $p<0.05$, and a significant Group × Phase interaction, $F(1,19) = 5.04$, $p<0.05$. This indicates that HVX did not significantly alter the amount of alcohol consumed, that alcohol intake varied with the concentration of alcohol presented and that differences among the groups depended on the concentration of alcohol presented. Post hoc tests revealed that HVX reduced the intake of 6% alcohol, $t(18) = 2.19$, $p = 0.02$, but not 3% alcohol, $t(18) = 0.01$, NS, and that ANG II reduced alcohol intake in both the HVX, $t(8) = 3.37$, $p<0.01$, and sham, $t(11) = 4.48$, $p<0.005$, groups. Figure 7b presents the mean water intake for the HVX and sham groups. A two-way analysis of variance with Group as the between subjects factor and Phase (3% alcohol and 6% alcohol) as the within subjects factor revealed a nonsignificant effect of Group, $F(1,19) = 1.80$, NS, a nonsignificant effect of Phase, $F(1,19) = 0.27$, NS, and a nonsignificant Group × Phase interaction, $F(2,38) = 1.16$, NS, indicating that HVX did not significantly alter the amount of water consumed and that water intake did not vary with the different phases of the experiment. Post hoc tests showed that water intake was increased by ANG II in both the HVX, $t(8) = -9.41$, $p<0.005$, and the sham groups, $t(11) = -5.41$, $p<0.005$. These findings indicate that HVX did not alter water intake or the ability of ANG II to stimulate water intake. The results of this experiment indicate that HVX alters alcohol intake under certain circumstances. HVX did not change the intake of 3% alcohol or modify the effect of ANG II on alcohol intake, but did reduce the intake of 6% alcohol. It may be that differences in the taste quality or pharmacological effect of 6%, but not 3%, alcohol may be more able to initiate vagus-related processes, and therefore the effect of HVX becomes evident at the higher alcohol concentration.

GENERAL DISCUSSION

Experiment 1 showed that GVX reduced voluntary alcohol intake. When offered a choice between an alcohol solution and water, animals subjected to GVX consumed less alcohol than the sham controls. This reduction was independent of alcohol concentration since the intake of both 3% and 6% alcohol was decreased. These results suggest that neural signals carried by the gastric vagus may play a role in the regulation of alcohol intake. Since ANG II reduced alcohol intake in both the GVX and sham-control groups, an intact gastric vagus is not necessary for ANG II to modify ethanol intake, and other peripheral sites are more likely to mediate this effect.

Total subdiaphragmatic vagotomy, which also severs gastric vagal efferents, increases the gastric retention of solid food (16). Food in the stomach reduces the rate of alcohol absorption which leads to a lowering of blood alcohol levels (7). This relationship was confirmed in the present study since the rate of alcohol absorption was slowed by GVX. A reduced rate of absorption and, therefore, a lowering of blood alcohol levels are not likely to have decreased alcohol consumption in the GVX group. Alcohol intake appears to be modulated inversely by blood alcohol levels (14). Therefore, a reduction in alcohol absorption would predict more, and not less, alcohol intake in the GVX group. Similarly, the finding that GVX enhanced alcohol metabolism is also not likely to have caused the reduction in alcohol intake in the GVX group. Therefore, the findings of the present experiments suggest that GVX did not alter alcohol intake through a change in alcohol pharmacokinetics.

Gastric vagotomy typically severs both afferent and efferent fibres. Efferent fibres in the gastric vagus control gastric motility and acid secretion (12). Therefore, the effect of severing these fibres on alcohol intake, would most likely be expressed through a change in alcohol pharmacokinetics. This possibility was not confirmed. Future experiments using atropine methyl nitrate could more directly test the relative contributions of gastric vagal afferents and efferents to voluntary alcohol intake.

In agreement with previous findings (23), GVX reduced the intake of a 20% sucrose solution. The intake of a saccharin solutions was also decreased by GVX indicating that GVX reduced the preference for sweet tasting solutions independently of the caloric value of the solution. However, GVX did not alter the intake of a salty solution. Since GVX reduced the intake of some flavored solutions and not others, the question of whether GVX also reduced alcohol intake through a change in taste function awaits the specific assessment of the effect of GVX on a substance with a taste similar to that of alcohol, but without its pharmacologic or caloric properties.

It is also possible that GVX produced a general state of malaise and thereby reduced alcohol intake. Total vagotomy, which also severs the gastric vagus, produces a conditioned taste aversion during the initial postsurgery period suggesting that vagotomy makes animals feel ill (24). If, in the present study, GVX reduced alcohol intake because it produced malaise, then this would predict that all consummatory behavior would be suppressed as well. However, GVX did not reduce the intake of a salty solution and, in fact, increased water intake. Therefore, it is unlikely that GVX reduced alcohol intake by producing a state of malaise.

GVX may have reduced alcohol intake in response to enhanced water intake. Decreased alcohol intake was accompanied by a stimulation of water intake in the GVX group. However, when offered limited access to a highly palatable sucrose or saccharin solution, gastric vagotomized animals consumed large quantities of both solutions indicating that they are capable of ingesting large quantities of fluid. This suggests that a relatively small increase in water intake cannot account for the observed reduction in alcohol intake.

Neural signals from the stomach to the brain, mediated by gastric vagal afferents, are thought to participate in the control of feeding (27). Gastric vagal afferents mediate some of the meal-contingent cues to the brain as indicated by the finding that GVX,

which interrupts gastric vagal afferents, reduces the intake of food (17). Therefore, the gastric vagus provides information to the brain regarding food intake which may be necessary for the initiation, maintenance or termination of feeding. Given that alcohol enters the stomach after it is consumed orally and that neural signals originating in the stomach are thought to send information to the brain concerning consummatory behavior, it is possible that gastric vagal afferents may relay information to the brain regarding alcohol consumption.

Previous work by Kulkosky *et al.* (10) showed the ability of total subdiaphragmatic vagotomy to reduce alcohol intake. In the present experiments severing the gastric branch of this nerve also reduced alcohol intake. Therefore, severing the gastric branch of the subdiaphragmatic vagus nerve is likely to have contributed to the effect observed in the Kulkosky *et al.* study. This finding emphasizes the importance of neural signals from the stomach to the brain in the regulation of alcohol intake.

In Experiment 2, rats subjected to HVX reduced their intake of 6% alcohol when offered a choice between water and a solution containing alcohol, although their intake of 3% alcohol was unchanged. Thus, the intake of a solution containing a higher alcohol concentration was reduced by HVX while the intake of a solution containing a lower alcohol concentration was not. ANG II reduced alcohol intake in both the HVX and sham groups suggesting that the hepatic vagus is not necessary for ANG II to reduce alcohol intake.

Since alcohol metabolism occurs primarily in the liver and hepatic vagal afferents have been shown to modify enzyme activity in the liver (26), it is possible that HVX may alter alcohol metabolism. A reduction in the ability of the liver to metabolize alcohol would require less alcohol intake to achieve a given blood alcohol concentration. Therefore, if HVX reduced alcohol metabolism, then the HVX group would reach their maximum blood alcohol levels with less alcohol intake than the sham group. Although this suggestion can explain why HVX reduced 6% alcohol intake in Experiment 2, it cannot account for the lack of an effect of HVX on 3% alcohol intake and is therefore probably not a complete explanation of the observed differences.

Neural signals carried by hepatic sensory fibres are thought to modify taste perception (21). Blake and Lin (2) found that information carried by the hepatic vagus can modify taste preferences. Furthermore, the palatability of a tastant can be enhanced by both alcohol and glucose intubation into the stomach (25), suggesting that visceral sensory output might modify taste perception in such a way as to strengthen alcohol consumption. Taken together, this suggests that HVX may have altered taste function so as to reduce the palatability of 6% alcohol. However, this explanation does not account for the lack of an effect on 3% alcohol intake. Higher alcohol concentrations may serve as stronger stimuli for hepatic sensory mechanisms. Therefore, the effect of HVX would only be seen at these higher concentrations. This possibility is supported by the finding that high concentrations of a glucose solution are indeed a more effective stimuli for suppressing hepatic vagal afferent firing than are low concentrations (19).

The present experiments suggest a relationship between mechanisms involved in the regulation of feeding and alcohol drinking behavior. Alcohol, as a drug, acts on the central nervous system producing a variety of pharmacological effects. However, the "food value" of alcohol may also be an important factor in modifying alcohol intake. The ability of a manipulation known to alter feeding to also affect alcohol intake is supported by this study since severing gastric vagal afferents, which are thought to participate in the regulation of feeding (27) reduced voluntary alcohol intake.

In summary, these experiments indicate that gastric vagotomy, and under certain circumstances hepatic vagotomy, can decrease alcohol intake. These manipulations are known to mediate neural information from the stomach and liver to the brain regarding the consumption of alcohol. The food-like properties of alcohol, as mediated by gastric and perhaps hepatic branches of the vagus nerve may serve a function in the regulation of alcohol intake.

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