Vasoactive Intestinal Polypeptide Response to Ethanol in Dogs

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MISAWA, T., ARAMAKI, J., CHIJIWA, Y., KABEMURA, T., NASU, T. and NAWATA, H. Vasoactive Intestinal Polypeptide Response to Ethanol in Dogs. Tohoku J. Exp. Med., 1990, 161 (1), 49-54 —— Only one report has described the ethanol-induced release of vasoactive intestinal polypeptide (VIP), and its mechanism of action is unknown. We studied changes in mesenteric immunoreactive VIP (IR-VIP) concentrations following the intrajejunal administration of 100 ml of normal saline, 5% and 10% ethanol, and hypertonic saline which was isoosmolar to 10% ethanol (1,670 mOsm/liter) in dogs. Administration of 5% and 10% ethanol resulted in significant and dose-dependent increases in mesenteric IR-VIP. Mesenteric IR-VIP changes and incremental integrated responses to 10% ethanol and to hypertonic saline were the same. We concluded that ethanol-induced VIP release in dogs is mainly due to ethanol's hyperosmolarity. ——— VIP; mesenteric vein; ethanol; hyperosmotic saline; osmotic pressure

Vasoactive intestinal polypeptide (VIP) is distributed throughout the gastrointestinal tract (Yanaihara et al. 1977; Fahrenkrug 1979) and nervous system (Said and Rosenberg 1976) and has a broad spectrum of biological activities. VIP's main role as a neurotransmitter in the gastrointestinal tract is the relaxation of smooth muscle and increase of blood flow. Several investigators have reported VIP-releasing factors (Schaffalitzky de Muckadell et al. 1977a; Bloom et al. 1978; Chayvialle et al. 1980a, b). Only the report by Schaffalitzky de Muckadell et al. (1977b) has shown a VIP-releasing effect of ethanol, and no report has demonstrated a mechanism of VIP release by ethanol. This study investigated the VIP response to intrajejunal ethanol administration by measuring IR-VIP concentrations in the jejunal mesenteric vein.

Material and Methods

Sixteen male mongrel dogs (weight, 13-18 g) were fasted for 24 hr. Anesthesia was induced by thiopental sodium (30 mg/kg) and maintained by barbital sodium (250 mg/kg).
A catheter with a cuff was placed 30 cm distal to the ligament of Treitz so that 100 ml of test solution could be administered as a bolus infusion. Test solutions included 5% and 10% ethanol, normal saline, and hypertonic saline were used in each of 4 dogs. Hypertonic saline had the same osmotic pressure (1,670 mOsm/liter) as 10% ethanol. Test solutions were adjusted to pH 7.0, and a catheter was placed in the mesenteric vein of the jejunum for blood sampling. After the operation, the dogs were left undisturbed for 60 min. Four-milliliter blood samples were collected in ice-chilled glass tubes containing 1.6 mg EDTA and 500 KIU aprotinin per ml of blood and were centrifuged at 3,000 rpm at 4°C. The plasma was lyophilized and stored at -20°C until the radioimmunoassay of plasma immunoreactive VIP (IR-VIP) was performed.

Plasma IR-VIP was measured using the radioimmunoassay technique we described previously (Chijiiwa et al. 1986; Misawa et al. 1986), and the antiserum (R-501) was a gift from Professor N. Yanaihara, Shizuoka College of Pharmacy. The maximum sensitivity of the assay was 1.6 pg/tube with a 95% confidence limit. The intraassay coefficient of variation was 6.6% and the interassay coefficient of variation was 15.1%.

Plasma IR-VIP values and incremental integrated VIP responses were expressed in terms of mean ± s.e. The unpaired Wilcoxon-test was used for statistical analysis, and p values less than 0.05 were regarded as significant.

**RESULTS**

The mean basal plasma IR-VIP concentration in the jejunal mesenteric vein was 223 ± 27 pg/ml (n = 16). Intrajejunal administration of normal saline did not change the mesenteric plasma IR-VIP concentration, but intrajejunal infusion of 5% or 10% ethanol induced a significant increase (Fig. 1). The increase in plasma IR-VIP induced by 10% ethanol was significantly higher than that induced by 5% ethanol at 7.5 and 15 min (p < 0.05). Therefore the plasma IR-VIP response to ethanol stimulation was dose-dependent. The peak mesenteric plasma IR-VIP concentration was 370 ± 28 pg/ml (1.8 times the basal level) in the 5% ethanol group and 480 ± 112 pg/ml (2.7 times the basal level) in the 10% group.

![Fig. 1. Changes in the mesenteric plasma IR-VIP concentration after intrajejunal administration of normal saline (□—□, n = 4), 5% (○—○, n = 4) and 10% (●—●, n = 4) ethanol. Each value represents the mean ± s.e. *p < 0.05 compared to each basal level.](image-url)
Fig. 2. Changes in the mesenteric plasma IR-VIP after intrajejunal administration of 10% ethanol (●—●, n=4) and hyperosmotic saline (○—○, n=4) adjusted to the same osmotic pressure as 10% ethanol. Each value represents the mean ± s.e. There were no significant differences between the 10% ethanol and hyperosmotic saline groups.

Fig. 3. Incremental integrated VIP response for 30 min after administration of normal saline (n=4), hyperosmotic saline (n=4), and 5% (n=4) and 10% (n=4) ethanol. Each value represents the mean ± s.e. *p < 0.05 compared to normal saline.
ethanol group. The plasma mesenteric IR-VIP concentration increased 2.2 times after the intrajejunal infusion of isoosmolar hypertonic saline (1,670 mOsm/liter), but the change in the IR-VIP concentration was not statistically significant. However, the change in the mesenteric IR-VIP concentration was the same following the intrajejunal administration of 10% ethanol and isoosmolar hypertonic saline (Fig. 2).

The incremental integrated IR-VIP response over 30 min following the administration of 10% ethanol was $7.3 \pm 2.6$ (ng/ml) × 30 min. The incremental integrated IR-VIP response in the groups receiving 10% ethanol and hypertonic saline ($6.9 \pm 3.0$ (ng/ml) × 30 min) was not statistically different (Fig. 3).

**DISCUSSION**

Several investigators have reported VIP releasing factors, including vagal stimulation (Schaffalitzky de Muckadell et al. 1977a), gastric distention (Chayvialle et al. 1980a), intraduodenal bile (Chayvialle et al. 1980b; Chijiwa et al. 1986), fat and acid (Schaffalitzky de Muckadell et al. 1977b; Bloom et al. 1978). However, conflicting data appeared when ethanol was used to stimulate VIP release. Schaffalitzky de Muckadell et al. (1977b) reported an elevation in peripheral plasma IR-VIP after the intraduodenal infusion of ethanol (vodka 86 proof), but Henry et al. (1981) reported that the introduction of 60 ml of vodka (86 proof) into an empty stomach did not increase peripheral IR-VIP in man. Jorde et al. (1979) reported a similar finding, that the intragastric infusion of 40% ethanol (60 ml) caused no change in peripheral IR-VIP.

We considered three explanations for the lack of an IR-VIP response to ethanol. The first, the venous plasma IR-VIP concentration in the stomach may be lower than in the duodenum, jejunum and ileum, and the same as in the peripheral vein (Misawa et al. 1986). Thus the oral administration of ethanol would not effectively stimulate IR-VIP release. The second, intragastric ethanol may flow slowly into the duodenum, resulting in little IR-VIP release from the duodenum or jejunum. The third reason is that 83.7% of VIP is degraded on the first transit through the liver (Kabemura et al. 1988). Therefore, the increase in peripheral plasma IR-VIP is less than the mesenteric concentration. To clarify the nature of the VIP response to ethanol in the gastrointestinal tract, it is necessary to measure changes in the IR-VIP concentration in the mesenteric or portal vein.

We found a dose-dependent increase in mesenteric plasma IR-VIP after intrajejunal infusions of 5% and 10% ethanol. Staub et al. (1981) have reported that the intravenous injection of ethanol causes an increase in peripheral plasma IR-VIP in man due to ethanol stimulation of the intracranial ganglia of the vagus nerve. However, we found that the basal peripheral IR-VIP concentration was $43 \pm 19$ pg/ml and the peak level was only $63 \pm 10$ pg/ml (not significant) after the intrajejunal administration of 10% ethanol in dogs (T. Misawa, unpublished).
We concluded, therefore, that the increase in mesenteric plasma IR-VIP originated from the jejunum and not from the central nervous system.

It has been reported that the intraduodenal infusion of 3% and 8% hypertonic saline increases peripheral plasma IR-VIP levels in dogs (Ebeid et al. 1977). If ethanol has the potent VIP-releasing factor except hyperosmolarity, the higher IR-VIP response would be seen after the intrajejunal administration of 10% ethanol than of hypertonic saline. But our data demonstrated that the pattern of IR-VIP release and the incremental integrated IR-VIP response after the intrajejunal administration of 10% ethanol and hypertonic saline was the same. Additionally while mechanical dilatation of the stomach has been shown to increase plasma IR-VIP (Chayvialle et al. 1980), in our hands, 100 ml of normal saline instilled into the jejunum did not increase mesenteric plasma IR-VIP.

We conclude that mesenteric plasma IR-VIP increases after the intrajejunal administration of ethanol primarily because of hyperosmolality of ethanol solutions.

References

