Ethanol exerts multiple actions on nearly all organs of the body, especially on the central nervous system and the gastrointestinal tract. However, little is known about the effects ethanol has on the brain-gut axis, the linkage between the central neural system and the autonomous innervation of the gastrointestinal tract. It is indisputable that ethanol consumption does affect e.g. exocrine pancreatic secretion or intestinal motility, but it is poorly understood, how alcohol consumption may disturb the brain-gut axis and how this may cause damage to gastrointestinal organs. Due to difficulties in directly assessing ethanol effects on the brain-gut axis in humans, animal models represent a versatile tool to study this topic. However, conventional animal models widely utilized in alcohol research, e.g. the Tsukamoto-French model or the Lieber-DeCarli model, do not mimic the human conditions of ethanol consumption and are therefore not suitable for studies of the brain-gut axis. Established models from other alcohol research disciplines, e.g. addiction research, are by far more applicable. Due to this reason, we have established an animal model of alcohol-dependent rats for the use in gastrointestinal alcohol research. In this model, rats are given free access to different of alcohol solutions (5% and 20% v/v) and tap water. Over time, the rats develop signs of alcohol dependence as seen in humans (e.g. deprivation effect). Organs isolated from rats exposed to this model are currently investigated in our laboratory for alcohol-related gene-regulation compared to non-alcoholic littermates. In addition, non-alcoholic components of alcoholic beverages might affect the brain-gut axis or possibly potentiate the toxicity of ethanol. In our model, commonly ingested alcoholic beverages such as beer, wine, cognac, vodka, and whisky and their non-alcoholic constituents will be tested in future animal studies.
INTRODUCTION

Alcohol-related diseases of the gastrointestinal tract play an important role in clinical gastroenterology. However, the mechanisms and pathophysiology underlying the effects of ethanol on the organs of the digestive tract are not yet completely understood. Besides of the causation of liver cirrhosis, chronic pancreatitis or neurological disorders, acute and chronic ethanol consumption may give rise to functional abnormalities of the digestive tract. These dysfunctions may be attributed to disturbances of the brain-gut axis, the linkage between the central neural system and the autonomous innervation of the gastrointestinal tract. Functional gastrointestinal disorders caused by a dysfunctional brain-gut axis are already very common in the normal population (1, 2), but alcohol consumption can even lead to higher prevalences of these disorders (3). In this clinical study by Fields et al., a collective of male alcoholic patients without apparent alcohol-related diseases of internal organs showed a significantly higher prevalence of symptoms of functional gastrointestinal (GI) disorders such as heartburn, chest and abdominal pain, nausea, vomiting, flatulence or diarrhoea compared to non-alcoholic controls especially during intoxication. Most GI symptoms could be diminished by abstinence, however a significant number of symptoms of functional GI disorders such as flatulence remained significantly more prevalent in alcoholics. Could a disturbance of the brain-gut axis be the cause for these symptoms, especially since the manifestations could not be attributed to apparent alcohol-derived organic diseases?

Strikingly, no studies have yet been conducted that directly investigate the impact of alcohol consumption on the brain-gut axis or exactly examine the role of the brain-gut axis in the development of alcohol-related gastrointestinal diseases in humans. However, a considerable number of the results of studies analyzing the effects of acute and chronic alcohol consumption on gastrointestinal organs may be attributed to a disturbance of the brain-gut axis (Tab. 1).

Animal models represent an essential tool to investigate alcohol-related diseases because they give researchers the opportunity to use methods that cannot be used in humans, such as knockout technology. However, there is still a need for new animal models resembling the human condition, especially for the investigation of complex research fields such as the brain-gut axis and its connection to alcohol-related gastrointestinal diseases.
In this article, we provide an overview of the findings about the possible role of the brain-gut axis in gastrointestinal alcohol research in humans and animals. We will also present a new animal model of alcohol-drinking rats that resembles the human condition of voluntary alcohol consumption.

Effect of ethanol on the central part of the brain-gut axis

Acute and chronic ethanol consumption exerts actions on or may even cause irreparable damage to the peripheral and the central nervous system, especially the brain. The neurological effects of alcohol can occur directly by neuronal cell damage due to ethanol toxicity, or indirectly by ethanol metabolites (e.g. acetaldehyde) or elevated serum levels of toxins (e.g. ammonia) derived from an impaired liver function due to alcoholic liver disease (4, 5). Prolonged ethanol abuse can cause focal lesions in certain areas or parts of the brain such as the cortex, the basal ganglia, the hippocampus, the cerebellum or the brain stem (5-7). The brain stem also contains the nuclei of the vagal nerve, which is an important part of the brain-gut axis. Surprisingly, no studies are available concerning the impact of ethanol consumption on the vagal nuclei in the brain stem such as the dorsal vagal nuclei or the nucleus tractus solitarii. In humans, direct studies of the effects of ethanol on the central portion of the brain-gut axis are not possible. In animals, direct application of ethanol into the cerebroventricular system (8) or by reverse microdialysis (9) into the vagal nuclei of the brain stem would be very helpful to examine the central effects of ethanol on the brain-gut axis. By means of intracerebroventricular administration of diverse substances, the research group of S.J. Konturek proved the importance of the brain-gut axis in the development of gastrointestinal diseases: Intracerebroventricular administration of bacterial lipopolyssaccharide (LPS) prevented the development of caerulein-induced pancreatitis by activation of sensory nerves and release of leptin, a peptide involved in the control of food intake (10). Further studies of this research group proved, that centrally

<table>
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<th>Organ function controlled by brain-gut axis</th>
<th>Ethanol-related gastrointestinal disorders</th>
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<td>Oesophageal motility</td>
<td>Gastrooesophageal reflux / reflux-oesophagitis</td>
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<tr>
<td>Gastric motility</td>
<td>Duodenogastral reflux / gastritis</td>
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<tr>
<td>Gastric mucosal defence</td>
<td>Increased mucosal haemorrhage (?)</td>
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<tr>
<td>Gut motility</td>
<td>Functional disorders (e.g. diarrhoea), increased mucosal damage</td>
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<tr>
<td>Pancreatic exocrine secretion</td>
<td>Chronic alcoholic pancreatitis (?)</td>
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Tab. 1. Possible disturbance of the brain-gut-axis by ethanol and causation of ethanol-related diseases of gastrointestinal organs.
administered leptin itself is protective against hyperstimulation-induced pancreatitis in the rat by reduction of Tumour Necrosis Factor (TNF)-alpha levels and by increase of Interleukin (IL)-4 production (11). Intracerebroventricularly administered leptin also protected against ethanol-induced gastric damage by activation of the vagal nerve and increase of gastric mucosal blood flow (12). These findings indicate that the central effects of ethanol itself might also play a key role in the development of ethanol-related disorders of the gastrointestinal tract via the brain-gut axis. Therefore, more studies on the central impacts of ethanol as well as alcoholic beverages on the brain-gut axis are required.

Evidence for disturbance of the brain-oesophageal axis by ethanol

Acute ethanol application exerts effects on the upper and lower sphincter as well as the peristalsis of the human oesophagus that may be attributed to a disturbance in the function of the autonomous nervous system (13, 14). Acute ethanol leads to a transient decrease in the lower oesophageal sphincter pressure and inhibition of the primary peristaltic movement of the distal oesophagus body causing impaired oesophageal clearance (14-16). Since intravenous application of ethanol also disrupts normal oesophageal motility it is presumed that the alcohol effect on the oesophagus has to be at least partially attributed to a systemic action conceivably also affecting the brain-gut axis (Fig. 1). These functional changes result in an increase in gastro-oesophageal reflux and the prolongation of each reflux episode by diminished oesophageal clearance (13). Chronic ethanol consumption induces secondary motility disorders in the distal oesophagus with
prolonged contractions of a higher amplitude than normal as well as simultaneous and double-peaked contractions. The effect on the lower oesophageal sphincter is opposite to that of acute ethanol administration (13). However, it is not known, whether these motility disorders can be solely imputed to a dysfunctional brain-gut axis. Especially the presence or absence of an alcoholic neuropathy in chronic alcoholics complicates the question whether a disorder can be attributed to a dysfunctional brain-gut axis or to the primary disease of the organ itself. Evidence for a disruption of the brain-gut axis due to chronic alcohol abuse is provided by the following findings: In alcoholics with an average daily ethanol consumption of up to 300 g over 18 years (and without any signs of neuropathy) the lower oesophageal sphincter pressure was significantly higher than in controls, with an intact relaxation cycle and reduced oesophageal clearance (17-19). In contrast, in patients with alcoholic peripheral neuropathy the lower oesophageal sphincter pressure was normal (20).

To further elucidate the impact of ethanol consumption on the origin of oesophageal diseases in humans numerous studies in animal models have been conducted. Ethanol-induced motoric dysfunction of the oesophagus, as seen in human alcoholics, was confirmed in a model of intravenous ethanol infusion in cats (21) and ethanol administration on isolated organs (22). Blood-borne ethanol produced a significant but dose-independent decrease of lower oesophageal sphincter pressure and amplitude (21). These actions were partially mediated by cholinergic stimulation, reversible and not caused by cytotoxicity (22). These results partly indicate a disturbance of the brain-gut axis by ethanol administration. In contrast to these acute ethanol effects, male cats accustomed to long-term ethanol consumption had significantly higher pressure and contraction amplitudes of the lower oesophagus especially in withdrawal phases but not for the period of chronic intoxication (23).

Despite great research effort, animal models could not yet sufficiently elucidate the mechanisms involved in ethanol-related oesophageal dysfunction. The investigation of the role of the brain-gut axis in alcohol-related oesophageal diseases requires further studies on the basis of more applicable animal models.

**Ethanol effects on the brain-gastric axis**

Up to now, exact studies on ethanol effects on the brain-gastric axis are lacking. For example, it is not known, if acute or chronic ethanol intoxication causes a central or peripheral impairment of the brain-gastric axis. It might be possible that a dysfunction of the brain-gastric axis caused by ethanol is partially responsible for the obvious derangement of gastric motility or impairment of the gastric defence against exogenous noxes leading to gastric haemorrhage (Fig. 2). Many studies have been carried out analyzing the impact of ethanol on gastric motility - with inconsistent results depending on dose and type of beverage studied and on the administration of a liquid or solid test meal (13). Ethanol
concentrations of 8 g/100 ml or more resulted in delayed gastric emptying when compared with water or low ethanol concentrations (24). In a study by Kaufmann and Kaye (25), gastric emptying was significantly inhibited by an isocaloric glucose control solution when compared with ethanol. While one group has shown that beer and white wine accelerated the gastric emptying of a high caloric liquid meal compared with water and equivalent ethanol concentrations (26, 27) examined the emptying of red wine and beer without a liquid or solid meal and showed that beer and red wine exerted an inhibitory effect on gastric emptying that was significantly higher than that obtained with an equivalent ethanol concentration.

While Keshavarzian et al. (28) did not see any influence of chronic alcohol abuse on gastric emptying of solid test meals 3-10 days after alcohol abstinence, Wegener et al. (29) found a dose-related inhibitory effect on the gastric emptying rate of solid test meals in actively drinking alcoholics.

It is obvious that more studies of the impact of alcoholic beverages and their non-alcoholic components on the brain-gut axis and gastric motility are required.

Animal studies have been more helpful to reveal the mechanisms responsible for the alteration of gastric motility by ethanol. Izbeki et al. (30) elucidated the role of the brain-gastric axis in the change of gastric motility by ethanol in rats. Acute ethanol administration (40% v/v) activated inhibitory capsaicin-sensitive afferent neurons of the N. vagus in the stomach leading to delayed gastric emptying. Blockade of these vagal nerve fibers completely blocked the effects of

Fig. 2. Schematic diagram of the effects of acute and chronic ethanol consumption on the brain-gastric axis. Acute and chronic ethanol administration lead to a decrease in mucosal barrier function, thus rendering the gastric mucosa sensitive to gastric acid, causing oxidative stress, infiltration by leukocytes and inflammation. As a side effect of mucosal injury, intramural innervation may also be damaged, leading to motility disorders. The brain-gastric axis clearly plays an important role in gastric mucosal protection against alcohol-induced damage, however, the effects of ethanol on the central parts of the brain-gastric axis has yet to be investigated (unpublished data).
ethanol on gastric motility. Another study in mice explicitly showed that chronic gastric administration of 40% ethanol (v/v) damages the intramural neurons of the stomach (31), which may impair gastric motility. These findings in animals imply that ethanol has profound effects on the peripheral part of the brain-gastric axis. However, none of these animal models mimics human alcohol consumption and its influence on the brain-gastric axis.

The role of the brain-gastric axis in ethanol-related change in gastric secretion and gastric damage in humans has also not been clearly defined yet. Effect of ethanol on gastric acid output is depending on concentration (13). Gastric instillation of 1.4% and 4.0% (v/v) pure ethanol had a small stimulatory effect on gastric acid output, with a response equivalent to 23% of the pentagastrin-stimulated maximal acid output (MAO). Higher concentrations of pure ethanol (up to 40% v/v) had either no effect or were slightly inhibitory (32). None of the ethanol concentrations tested increased plasma gastrin concentrations (32); for reviews, see Chari et al. (33, 34), Teyssen and Singer (35), and Singer (36). In contrast, alcoholic beverages produced by fermentation, such as beer and wine, are potent stimuli of gastric acid output as well as the release of gastrin (32, 37). On the other hand, beverages with a higher alcohol content that are produced by distillation, such as whisky (40% v/v) and cognac (40% v/v), do not stimulate gastric acid output or the release of gastrin (32). Experiments by our group have shown that the substances responsible for the maximal gastric acid secretion in the fermented beverages are succinic acid and maleic acid, both of which are produced during the process of alcoholic fermentation, and that gastrin does not mediate their effect (38). Interestingly, solutions of pure ethanol (4%, 10%, 40% v/v) caused more severe gastric haemorrhage than the corresponding alcoholic beverages (beer, wine, whiskey) (39). This also implies a crucial role of non-alcoholic components of these beverages. Studies on the impact of non-alcoholic ingredients on the brain-gastric axis do not yet exist.

However, studies in rats clearly showed a direct connection between the brain-gastric axis and gastric defence against ethanol-derived damage. Leptin and cholecystokinin, both centrally and peripherally active peptides in the brain-gut axis, proved to be powerful substances in gastroprotection against damage induced by 75 - 100% (v/v) ethanol (12, 40, 41). A further important role in gastric protection against ethanol damage plays the vagal nerve as another part of the brain-gastric axis (42). However, studies investigating the effect of ethanol consumption resembling the human condition and its impact on the brain-gastric axis are completely lacking and need to be conducted in suitable animal models.

Ethanol effects on the brain-gut axis - small and large bowel

Studies on the explicit role of the axis between the brain and the small and large bowel and ethanol-related disorders of these organs do not exist. Common ethanol-related effects on the gut are (i) mucosal damage of the upper small
intestine, thereby contributing to the qualitative and quantitative malnutrition frequently observed in alcoholics, (ii) alterations in the bacterial flora and (iii) increased gut permeability possibly resulting in endotoxemia and subsequent liver damage (43) (Fig. 3). Even a single acute alcohol binge can cause mucosal damage in the upper small intestine. Chronic alcohol abuse additionally inhibits water and sodium absorption in the small intestine, one cause of diarrhoea in alcoholics (43). By mucosal injury, ethanol could also have an impact on the enteric nervous system or neurohormonally active cells in the intestinal mucosa. Therefore, dysfunction of the brain-gut axis may play a role in ethanol-derived motility disorders. Unfortunately, inconsistent results of studies analyzing the effects of acute ethanol administration on small bowel motility do not permit any conclusions (43). Chronic ethanol consumption caused an inhibition in bowel motility (29, 44), but a direct involvement of the brain-gut axis was not shown.

Most of the recent concepts concerning the pathophysiological sequelae of ethanol effects on gut morphology and function in humans are based on findings in animal models (Fig. 3). In diverse animal models acute as well as chronic...
ethanol administration dose-dependently led to microvascular stasis, increased transcapillary fluid and protein loss, epithelial oedema, blebs at the tips of the villi, villus shrinking, rupture of intra-epithelial junctions and increase in epithelial permeability for macromolecules including endotoxin (45-52). One study also examined the impact of ethanol on the enteric nervous system of the gut: Acute ethanol (10 - 300mM) selectively inhibited NMDA type excitatory amino acid receptors in ileal myenteric plexus of guinea pigs similarly to NMDA receptors in the CNS (53). Another reason why acute ethanol may affect intestinal motility was shown in a model of intraperitoneal ethanol administration in rats. The production of contractile proteins in the jejunum and ileum was significantly lower compared to saline-treated control (54, 55). This aspect may contribute to acute intestinal disorders (e.g. diarrhoea) frequently seen after binge drinking in humans. In contrast to findings in the stomach, chronic ethanol feeding (3% v/v for 8 weeks) did not affect the motility of the ileum in rats (56).

Animal Studies of the effect of ethanol consumption resembling the human condition and its impact on the axis between the brain and the small and large bowel are not yet available.

**Ethanol effects on the brain-pancreatic axis**

Acute as well as chronic ethanol administration has profound effects on the exocrine function of the pancreas (Fig. 4). Chronic ethanol consumption may damage the organ leading to chronic pancreatitis. The mechanisms leading to this disease are not yet completely understood. The pancreas is the only other peripheral organ apart from the gut that has a significant intrinsic nerve plexus (57). Its exocrine and endocrine functions are widely controlled by the brain-pancreatic axis consisting of several hormonal and neural feedback mechanisms (58). Therefore, interference of acute and chronic ethanol administration with the brain-pancreatic axis seems to be very likely. Oral or intraduodenal ethanol causes a moderate stimulation of pancreatic bicarbonate and enzyme output, intravenous ethanol inhibits basal and hormonally stimulated pancreatic exocrine secretion in humans, dogs, cats, pigs, rabbits, and rats (59, 60). This inhibition could be mediated by the brain-pancreatic axis, i.e. inhibitory cholinergic mechanisms, or be the result of a direct cellular effect of ethanol. In vitro investigations have specified several important signalling molecules of the brain-pancreatic axis that may be involved in the action of ethanol on stimulus-secretion coupling in the exocrine pancreas, such as cyclic adenosine monophosphate, intracellular calcium, and cholecystokinin and somatostatin receptors (60). In difference to pure ethanol solutions and distilled spirits, beer strongly stimulates pancreatic enzyme output, probably by non-alcoholic fermentation products. This has still to be investigated. During chronic alcoholism, the ethanol-induced inhibition is replaced by an enhanced enzyme output that causes intraductal protein precipitation. *In vitro* investigations suggest...
that this increase is reversible after alcohol withdrawal. The occurrence of protein precipitates is considered to be a crucial step in the development of chronic alcoholic pancreatitis in humans. Other ethanol-induced secretory alterations that may contribute to the development of alcoholic pancreatitis are (i) a decreased secretion of trypsin inhibitor, (ii) an increased cholinergic tone, and (iii) changes in the concentration of lithostathine.

Animal studies in dogs and rats showed a cholinergic inhibitory effect of acute ethanol administration on pancreatic exocrine secretion that was probably mediated also in the CNS (61, 62). Recently, Konturek and co-workers clearly proved a key role of the brain-pancreatic axis in the development of caerulein-induced pancreatitis (10, 11). Furthermore, animal models of chronic ethanol administration also demonstrated that the brain-pancreatic is highly relevant for the development of alcoholic pancreatitis: Chronically ethanol-fed rats treated with cholecystokinin-octapeptide causing hypersecretion showed significantly more severe pancreatic injury than non-alcoholic littermates (63); for review see Schneider et al., (64).

Fig. 4. Schematic diagram of the role of the brain-pancreatic axis in alcohol-related organ damage. Acute and mainly chronic alcohol consumption may cause pancreatic injury by intraglandular enzyme activation, followed by leukocyte recruitment, oxidative stress, decrease of blood flow and inflammation, causing chronic alcoholic pancreatitis. The brain-pancreatic axis plays a very important role in alcohol-derived (hyper-) secretion of the gland. However, the exact mechanisms remain still to be unravelled (unpublished data).
Although the pancreas is probably the best examined organ concerning the role of the brain-gut axis in ethanol-related intestinal diseases, an enormous number of unsolved questions still exists. An animal model resembling the human condition of ethanol consumption could be very useful, e.g. to examine the impact of alcoholic beverages on the brain-pancreatic axis and its role in development of chronic alcoholic pancreatitis.

A new animal model in gastrointestinal alcohol research

Recently, Spanagel and co-workers developed a new animal model in rats to study the neurobiological and molecular mechanisms of alcohol dependence (65, 66). In this model, rats are given the free choice between tap water and two different ethanol solutions to mimic human drinking behaviour (5% and 20% v/v, resembling the ethanol content of beer and hard liquor, respectively) in a long-term time frame (6 month or longer) (Fig. 5). The basal voluntary ethanol intake lies between 2.5 - 3.5 g x kg\(^{-1}\) x d\(^{-1}\), that resembles moderate alcohol consumption in humans. A very important aspect of this model are repeated withdrawal (deprivation) phases of two weeks, during which the animals only have access to tap water but not to alcohol solutions. The renewed availability of alcohol solutions leads to a pronounced but temporary increase in voluntary alcohol intake and preference (67, 68) (Fig. 6). This robust phenomenon is called the alcohol deprivation effect (ADE) and is observed across several species including rats, mice, monkeys, and humans (69-71). Another important feature of this

Fig. 5. Rat model of long-term voluntary ethanol consumption with repeated deprivation and stress phases. Rats have free access to tap water, 5% and 20% ethanol solutions (resembling e.g. beer and hard liquor). Over time they develop certain criteria also found in human alcoholics, such as craving, relapse, loss of control or signs of physical withdrawal.
model are repeated stress procedures (e.g. forced swimming in cold water) that lead to transient elevated ethanol intake (Fig. 7) and are thought to enhance the development of alcohol dependence (66). This model is widely accepted in alcohol addiction research and features a broad range of characteristics of human alcoholics: Rats obtained from this model (i) have an incentive demand to consume alcohol, (ii) exhibit relapse-like drinking even after a very long time of abstinence, (iii) show tolerance to alcohol and have mild signs of physical withdrawal during the onset of abstinence, and (iv) during abstinence they also exhibit a psychological withdrawal syndrome consisting of enhanced anxiety-related behaviour and hyperreactivity to stressful situations (72). The model also proved to be helpful in analyzing the influence of stress and genetic background of rats on alcohol drinking behaviour and development of alcohol dependence (73, 74).

Until now, no morphologic or functional examinations of organs of the gastrointestinal tract or the linkage between the brain and the gastrointestinal organs had been performed in this model. Furthermore, no animal model does yet exist that offers the opportunity to study ethanol-dependent changes of one or more different organs or organ systems (especially the gastrointestinal tract), in alcohol-dependent experimental animals at the same time. Existing animal models in gastrointestinal alcohol research, such as the Tsukamoto-French model of constant intragastric ethanol infusion or the Lieber-DeCarli diet (an alcohol feeding regimen) have provided great insight in molecular mechanisms of e.g. alcoholic liver disease, but they are completely lacking the physiology of human drinking behaviour (75). Therefore, we adapted this model of alcohol-dependent rats for gastroenterology research to examine organs such as the oesophagus, the stomach, the gut, the pancreas and the liver, in regard to ethanol-related

Fig. 6. Alcohol deprivation effect (ADE) in Wistar rats. Ethanol withdrawal for 14 days leads to a marked increase in both, 5% (v/v) and 20% (v/v) ethanol intake after return of the ethanol solutions in normal Wistar rats in our animal model of voluntary ethanol consumption (unpublished data).
pathophysiological and functional changes. Organs isolated from rats exposed to this model are currently investigated in our laboratory for alcohol-related gene-regulation compared to non-alcoholic littermates. Thus, this model could be perfectly used to examine the effects of acute and chronic ethanol administration on the brain-gut axis or what impact a possible disruption of the brain-gut axis by ethanol has on the development of gastrointestinal disorders.

Future research perspectives

Acute and chronic ethanol consumption may affect the brain-gut axis thus contributing to ethanol-related diseases of the gastrointestinal tract. However, direct studies of this topic are scarce or are lacking completely, depending on the type of organ. Because of the complex interaction between central and peripheral mechanisms leading to the disturbance of the brain-gut axis by ethanol, the utilization of our new animal model that mimics human alcohol consumption could be very valuable.

Because non-alcoholic components of alcoholic beverages proved to have an important impact on gastrointestinal organs, commonly ingested alcoholic beverages such as beer, wine and hard liquors on the brain-gut axis will also be tested in this model and a systematic analysis of the particular effects of the non-alcoholic constituents on the brain-gut axis has to be carried out.

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