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Appetite-Regulating hormones block alcohol cravings

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Abstract
Alcohol is commonly viewed as a psychoactive substance that primarily affects brain function. The effects of alcoholism on modern society are vast and deeply rooted in our history. Alcohol consumption causes problems at the individual, social, health and financial level. An alcohol craving is an intense desire or compulsion to drink alcohol. There exist commonalities between over-eating and over-consumption of alcohol. Evidence is growing that appetite regulating peptides such as leptin and ghrelin are altered in alcoholism. The neuropeptides leptin and ghrelin are involved in the appetite regulating network consisting of distinct orexigenic (ghrelin) and anorexigenic (leptin) circuitries. Recently, it was suggested that these hormones, ghrelin and leptin may play a role in alcohol use disorders. Therefore the goal of this review is to discuss the results of some recent investigations of the potential interactions of these systems with acute and chronic alcohol responses and the potential treatment for alcohol dependence.

Keywords: alcoholism, craving, ghrelin, leptin, drug dependence

Introduction

Alcoholism is a condition in which an individual becomes dependent on alcohol. Dependence on alcohol interferes with the individual's day to day activities along with his personal and professional life. Alcoholism has deleterious effects on one's overall health. Organs such as the brain, liver, heart, kidneys and stomach are most affected. Drinking alcohol during pregnancy causes damage to the brain of the unborn child.

Alcoholism is the most severe form of alcohol abuse and involves the inability to manage drinking habits. It is also commonly referred to as alcohol use disorder. Alcohol use disorder is organized into three categories: mild, moderate and severe. Each category has various symptoms and can cause harmful side effects. Individuals struggling with alcoholism often feel as though they cannot function normally without alcohol. This can lead to a wide range of issues and impact professional goals, personal matters, relationships and overall health. Over time, the serious side effects of consistent alcohol abuse can worsen and produce damaging complications.

- **Common signs of alcoholism include**
  - Spending a substantial amount of money on alcohol
  - Being unable to control alcohol consumption
  - Craving alcohol when you're not drinking
  - Feeling the need to keep drinking more
  - Behaving differently after drinking
  - Putting alcohol above personal responsibilities
- **Several short-term effects of alcohol abuse may produce**
  - Slow reaction time
  - Reduce brain activity
  - Lowered inhibitions
  - Restlessness
  - Blurry vision
  - Difficulty breathing
- **Here are some of the long-term health conditions caused by alcohol**
  - Brain defects
  - Wernicke-Korsakoff syndrome (a neurobiological disease)
  - Bone loss
  - Liver disease
  - Heart problems
  - Increased risk of cancer
  - Vision damage
  - Diabetes complications

An alcohol craving is an intense desire or compulsion to drink alcohol. When people are actively drinking, cravings keep them locked in the vicious cycle of addiction. During active addiction, people will give in to cravings and continue to drink because it keeps their blood alcohol level to a point where they won't experience the symptoms of withdrawal.

Fig 1: Effect of alcoholism on body [6]

It is well known that alcohol ingestion may serve as an appetizer causing increased food intake in both normal weight and obese individuals. There exist commonalities between over-eating and over-consumption of alcohol. Like alcoholism, obesity and binge eating are complex genetic traits determined by several genes, and interacting with the environment. For example, sweet liking has been proposed as a possible endophenotype for alcohol dependence (AD) and a link between glucose levels and alcohol-seeking behavior has been suggested both in animals and in alcohol-dependent individuals. Furthermore, it has been suggested that feeding-related peptides, such as leptin, thyroid hormones are related to alcohol-seeking behavior. In recent years there has been a growing interest in the possible role of the feeding-related peptide ghrelin in AD.

Ghrelin, commonly referred to as the "hunger hormone," is a 28-aminoacid peptide known primarily for its role in increasing appetite and food intake. Ghrelin hormone is produced and released mainly by the stomach with small amounts and also released by the small intestine, pancreas, brain. This orexigenic peptide hormone was discovered in 1999. Ghrelin act as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), a G-protein coupled receptor that induces growth hormone (GH) release from the pituitary. Ghrelin stimulates appetite by acting on the hypothalamic arcuate nucleus (ARC), a region that controls the intake of food and other substances, including alcohol. Ghrelin is able to stimulate food-seeking behavior. Alcohol craving and food-seeking behavior are supposed to share common underlying neural circuits.

Leptin is a feeding-related 146-amino acid peptide produced by adipose tissue that may also have a role in AD. Serum leptin levels are altered in AD individuals and associated with increased craving for alcohol.

Leptin and ghrelin have inverse appetitive effects; leptin decreases appetite, food intake and reward, whereas ghrelin exhibits opposite roles on these behaviors. Both peptides act as afferent signals to the hypothalamus, leptin and ghrelin receptors are also expressed in motivation reward brain regions linked to food-related behaviors such as ventral tegmental area and substantia nigra that signal via dopaminergic neurons to cortical and limbic region involved in motivational response to both food and drugs [1, 2, 3, 4, 5].

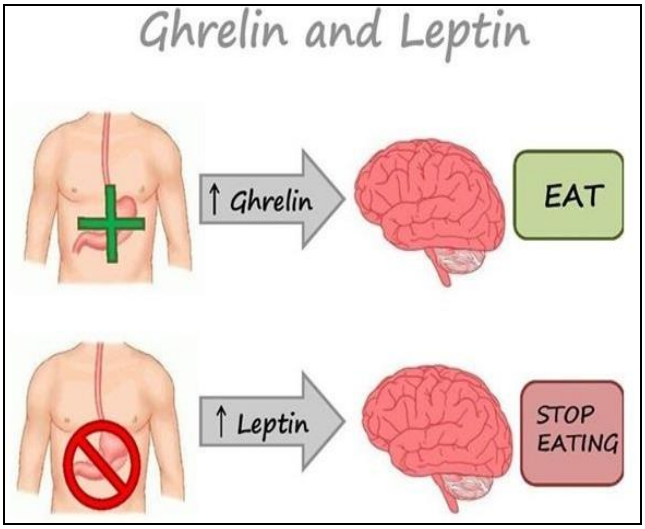

Fig 2: Effect of Ghrelin and Leptin on appetite [7]

Pharmacological Aspects of Ghrelin

The ghrelin cell is also known as an A-like cell (pancreas), X-cell (for unknown function), X/A-like cell (rats), Epsilon cell (pancreas), P/D sub 1 cell (humans) and Gr cell [8]

Location

Ghrelin cells are found mainly in the stomach and duodenum, but also in the jejunum, lungs, pancreatic islets, gonads, adrenal cortex, placenta, and kidney. It has recently been shown that ghrelin is produced locally in the brain [9, 10, 11].

Features

Ghrelin cells are found in oxyntic glands (20% of cells), pyloric glands, and small intestine. They are ovoid cells with granules. They have gastrin receptors. Some produce nesfatin-1. Ghrelin cells are not terminally differentiated in the pancreas: they are progenitor cells that can give rise to A-cells, PP cells and Beta-cells there [12, 13, 14, 15, 16].

Mechanism of action

Pancreas

Ghrelin inhibits glucose-stimulated insulin secretion from beta cells in the pancreatic islets. Ghrelin does this indirectly by promoting local negative feedback mediated by somatostatin from pancreatic delta cells, which selectively express the ghrelin receptor [17].

Glucose metabolism

The entire ghrelin system (dAG, AG, GHS-R and GOAT) has a gluco-regulatory action [18].

Pharmacological Aspects of Leptin

Predominantly, the "energy expenditure hormone" leptin is made by adipose cells, thus it is labeled fat cell-specific. In the context of its effects, it is important to recognize that the short describing words direct, central, and primary are not used interchangeably. In regard to the hormone leptin, central vs peripheral refers to the hypothalamic portion of the brain vs non-hypothalamic location of action of leptin; direct vs indirect refers to whether there is no intermediary, or there is an intermediary in the mode of action of leptin; and primary vs secondary is an arbitrary description of a particular function of leptin [19].

Fig 3: A comparison of a mouse unable to produce leptin, resulting in obesity, constant hunger, and lethargy (left), and an active normal weight mouse (right)

Location of action

Leptin acts directly on leptin receptors in the cell membrane of different types of cells in the human body in particular, and in vertebrates in general. The leptin receptor

is found on a wide range of cell types. It is a single-trans membrane domain type I cytokine receptor, a special class of cytokine receptors. Further, leptin interacts with other hormones and energy regulators, indirectly mediating the effects of: insulin, glucagon, insulin-like growth factor growth hormone, glucocorticoids, cytokines, and metabolites [20, 21].

Mechanism of action

The central location of action (effect) of the fat cell-specific hormone leptin is the hypothalamus, a part of the brain, which is a part of the central nervous system. Non-hypothalamic targets of leptin are referred to as peripheral targets. There is a different relative importance of central and peripheral leptin interactions under different physiologic states, and variations between species [21].

Function

The primary function of the hormone leptin is the regulation of adipose tissue mass through central hypothalamus mediated effects on hunger, food energy use, physical exercise and energy balance. Outside the brain, in the periphery of the body, leptin's secondary functions are: modulation of energy expenditure, modulation between fetal and maternal metabolism, and that of a permissive factor in puberty, activator of immune cells, activator of beta islet cells, and growth factor.

Leptin, the "Stop Appetite Hormone"

The opposing hormone to ghrelin is the stop appetite hormone, leptin. Leptin is a hormone produced in the fat cells. It plays a role in regulating body weight by signaling the brain to reduce appetite and burn more calories. Leptin is a primary modulator of body weight and metabolism, and it mediates weight-loss by decreasing hunger and food consumption and increasing energy expenditure. Yet, some studies have shown that losing weight causes a marked decrease in leptin levels, which may in turn increase appetite. Counter to what would be anticipated; obesity is linked to unusually high concentrations of leptin. Some research suggests that these high concentrations make the receptors for leptin inactive and impair the very mechanism that should eliminate excess fat. Then, although plenty of leptin is produced, the body's appetite suppression system is unable to function properly

Leptin and Ghrelin Levels and Their Relation with Alcohol Craving

L. Leggio *et al* found that intravenous ghrelin administration significantly reduced serum leptin levels compared with placebo and that there was an inverse relationship between ghrelin and leptin, in that the higher the serum concentration of ghrelin, the lower the concentration of leptin.

The researchers also found that higher concentrations of ghrelin in the blood meant more severe cravings for alcohol. In contrast, leptin acted to curb alcohol cravings. Placebo had no effect on leptin or ghrelin concentrations or cravings. It's either the higher levels of ghrelin or the lower levels of leptin, but more probably it is the interaction, the cross talk between these two hormones, that is affecting alcohol craving.

Another study showed that appetite-regulating peptides may be of special importance regarding alcohol craving in subtypes of patients. In that patients were classified according to Lesch's typology of alcohol dependence and according to their preferred type of alcoholic beverage. They found a significant positive association for leptin in patients of Lesch's types 1 and 2, and in patients consuming beer or wine. Ghrelin levels showed a significant trend regarding an association with craving in patients of Lesch's type 1.

The Role of Ghrelin Signaling in Drug Dependence

Data from several publications reviewed herein suggest that ghrelin signaling has an important role for reward in general. The intravenous administration of ghrelin in body shows increased locomotor stimulation mediated by cocaine in rats . This data shows that there is a positive correlation between increased level of ghrelin and increased cocaine seeking behavior in rats.

Pharmacological suppression of GHS-R1A by means of JMV2959 reduces the rewarding properties of amphetamine and cocaine as measured by locomotor stimulation, accumbal dopamine release and conditioned place preference. In addition, either genetic or pharmacologic suppression of GHS-R1A attenuates cocaine induced locomotor stimulation as well as sensitization in rats. Food restriction, which elevates ghrelin levels, augments amphetamine- and cocaine-induced hyperlocomotion, enhances cocaine-seeking behavior and increases self-administration of cocaine or amphetamine in rats. Furthermore, the GHS-R1A antagonist JMV2959 decreases the rewarding properties of nicotine as well as prevents nicotine induced locomotor sensitization in rodents.

Potential Treatment of Alcoholism

Ghrelin is responsible for the alcohol dependence in humans. As the level of ghrelin in the body increases, it increases the alcohol consumption or desire to consume alcohol which is called as alcohol craving. So, if the ghrelin's actions are blocked, the urge of an individual towards the alcohol will be reduced. And if it is continuously treated with the same treatment, it may help an individual to quit the alcohol or any specific drug dependence. For that purpose, the drugs such as ''Ghrelin receptor'' (GHS-R1A) antagonist like JMV2959 can be used.

These Ghrelin receptor antagonists are administered to block the action of ghrelin and eventually help to decrease the effect of ghrelin.

The data show that mice treated with ghrelin increase their alcohol consumption. When ghrelin's actions are blocked by administering ghrelin receptor antagonists such as JMV2959, mice no longer show preference for an alcohol-associated environment - in other words, alcohol is no longer able to produce its addictive effects that include reward searching behavior.

Also these drugs can be used to treat the over eating disorder. Due to this, the obesity of the patients caused by such disorders can be treated without any surgeries.

Conclusion

Alcohol use disorder is one of the major causes of illness and death in society, and the economic costs are extensive. Only a few medications are approved for treatment of alcohol dependence and clinical trials suggest that the effect of these pharmacological agents is moderate. There is

therefore a need for additional and more effective medications. Ghrelin administration acutely decrease blood leptin levels and that decrease in leptin correlated with an increase craving for alcohol. Antagonizing the ghrelin system might lead to a new and innovative way to provide an effective treatment for AD. However, future studies may explore the potential of blocking ghrelin signaling as a new promising treatment for alcoholism.

Ghrelin should be considered together with other recent candidate hormones that potentially have roles in alcoholism, such as leptin-Ghrelin should be considered together with other recent candidate hormones that potentially have roles in alcoholism, such as leptin Ghrelin should be considered together with other recent candidate hormones that potentially have roles in alcoholism, such as leptin Ghrelin should be considered together with other recent candidate hormones that potentially have roles in alcoholism, such as leptin Ghrelin should be considered together with other recent candidate hormones that potentially have roles in alcoholism, such as leptin.

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