Psychoneuroendocrinology (2013) 38, 3085—3091

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Fasting-induced increase in plasma ghrelin is blunted by intravenous alcohol administration: A within-subject placebo-controlled study

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Received 6 August 2013; received in revised form 5 September 2013; accepted 6 September 2013

KEYWORDS
Alcohol;
Ghrelin;
Insulin;
GLP-1;
PYY;
Intravenous alcohol administration

Summary Ghrelin is a 28-amino acid peptide produced mainly by mucosal neuroendocrine cells lining the fundus of the stomach. Preclinical and clinical studies suggest that ghrelin plays a role in alcoholism. Furthermore, human laboratory studies indicate that acute oral administration of alcohol results in reduced circulating ghrelin. As ghrelin is primarily produced in the stomach, one question never previously explored is whether alcohol administered intravenously (IV) results in similar decrease in ghrelin levels. Thus, this study analyzed the potential effects of IV alcohol administration on plasma ghrelin levels in healthy nonsmoking social drinkers ($n = 44$) who received either a 180-min IV infusion of 6% (v/v) alcohol or 0.9% normal saline in two separate counterbalanced sessions. At each session, participants arrived having fasted for ~7 h and received a light breakfast 60 min before the infusion. The percent change (%Δ) in ghrelin levels was 4.5-fold less in the alcohol condition than the saline condition. In fact, there was only a modest change in ghrelin levels from baseline in the IV alcohol condition (9.6%Δghrelin) while in the IV saline condition there was a robust change (43.4%Δghrelin). There was a trend toward significance in %Δghrelin in the alcohol condition compared to the placebo condition

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0306-4530/$ — see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.psyneuen.2013.09.005

(F[1,33] = 3.3, p = 0.07). While the exact mechanisms by which alcohol influences ghrelin levels are unclear, alcohol may act directly in the stomach by inhibiting ghrelin secretion and/or release, and may also attenuate ghrelin levels systemically. Although IV alcohol did not reduce circulating ghrelin levels, as seen in previous studies with oral alcohol administration, the present findings suggest that, despite bypassing the stomach, alcohol still attenuated circulating ghrelin levels, i.e. the fasting-induced increase in circulating ghrelin was blunted by IV alcohol administration. These findings lead us to hypothesize that alcohol might affect ghrelin signaling not only via a local effect on the stomach mucosa, but also via a systemic effect.
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1. Introduction

Ghrelin is a 28-amino acid peptide produced mainly by mucosal neuro-endocrine P/D1 cells lining the fundus of the human stomach, and acts as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R1a) (Inui et al., 2004; Kojima et al., 1999). Ghrelin activates hypothalamic orexigenic neurons and inhibits anorectic neurons to induce hunger (Toshinai et al., 2003). Accordingly, ghrelin stimulates feeding in animals (Tschop et al., 2000) and humans (Druce et al., 2005). Additionally, GHS-R1a's are also highly co-expressed with dopamine receptors in other brain regions [e.g., midbrain, raphe nuclei and ventral tegmental area (Katayama et al., 2000; Zigman et al., 2006)], suggesting that ghrelin modulates reward processing.

Consistent with the literature on the role of ghrelin in food reward (Dickson et al., 2011; Schellekens et al., 2012) and with the known overlap in pathways regulating food and alcohol intake (Leggio et al., 2011; Tomasi and Volkow, 2013), a growing body of preclinical and clinical literature [*reviewed in:* (Leggio, 2010)] suggests that ghrelin is involved in alcohol reward and plays an important role in alcohol-related seeking behals, e.g. locomotor activity, dopamine release, conditioned place preference, and free-choice drinking in rodents (Jerlhag et al., 2009, 2011; Landgren et al., 2012), as well as alcohol craving and consumption in humans (Addolorato et al., 2006; Koopmann et al., 2012; Leggio et al., 2012).

Given the link between ghrelin and alcohol-related behaviors, an important question that has been investigated is how alcohol affects blood ghrelin levels. Studies with alcohol-dependent patients indicate that blood ghrelin levels are lower in actively drinking alcoholic patients (Addolorato et al., 2006; Badaoui et al., 2008; de Timary et al., 2012; Koopmann et al., 2012; Leggio et al., 2012) and higher in those who are abstinent (de Timary et al., 2012; Kim et al., 2005, 2013; Koopmann et al., 2012; Kraus et al., 2005; Leggio et al., 2012; Wurst et al., 2007). Findings with alcohol-dependent patients, however, are not without inconsistencies, probably due to several differences across studies [e.g., differences in metabolic conditions and control groups; see also: (Leggio, 2010)]. One of the potential issues to consider is that in most of these studies with alcoholic patients, the ''actively drinking'' or ''abstinent'' status of the patients was primarily based on self-reported data. A few placebo-controlled human laboratory studies have provided more accurate information, at least on the effects of an acute oral administration of alcohol on blood ghrelin levels. Specifically, Calissendorff and colleagues (Calissendorff et al., 2005) conducted a within-subject controlled study in eight healthy individuals who consumed alcohol (0.55 g/kg) during one session and water in another counterbalanced session. Compared to baseline, blood total ghrelin levels significantly decreased after consuming alcohol, while no changes were observed after drinking water. The same group replicated these results in two subsequent studies (Calissendorff et al., 2006, 2012), one of which demonstrated that both total and active ghrelin levels continued to significantly decline after alcohol ingestion (Calissendorff et al., 2006). In another within-subject, counterbalanced controlled study by Zimmermann and colleagues (Zimmermann et al., 2007), nine healthy men consumed 0.6 g/kg alcohol mixed with grapefruit juice on one day and a matched volume of grapefruit juice on another day. Ghrelin levels rapidly and significantly declined after drinking the alcoholic beverage, reaching 66% below baseline after 75 min and remained at this level for the duration of observational period (120 min). Furthermore, ghrelin levels were lower after consuming the alcoholic drink compared to the non-alcoholic juice. In summary, human laboratory studies conducted with rigorous experimental designs and under well-controlled conditions have consistently shown that oral administration of alcohol results in reduced circulating ghrelin. These studies have all examined changes in ghrelin levels after an oral alcohol administration (Calissendorff et al., 2005, 2006, 2012; Zimmermann et al., 2007). Given that ghrelin is primarily produced in the stomach (Inui et al., 2004), an additional question never explored is whether bypassing the gastrointestinal tract by using alcohol administered intravenously (IV) has the same inhibitory effect on ghrelin levels. Therefore, the goal of this study was to analyze the potential effects of IV alcohol administration on plasma ghrelin levels. In addition to ghrelin, we also assessed other related appetitive peptides, namely insulin, glucagon-like peptide 1 (GLP-1), and Peptide YY (PYY) in order to explore if IV alcohol may also affect these other hormones.

2. Methods

2.1. Study population

Participants were healthy nonsmoking social drinkers recruited for a laboratory study, approved by the Institutional Review Board at the National Institutes of Health (NIH), investigating age × gender interactions on the effects of IV alcohol administration. Details of the main study were reported in Vatsalya et al. (2012). In brief, potential participants were evaluated by a screening consisting of medical history, physical exam, electrocardiogram and laboratory tests. Participants were stratified by gender and age (young [21–25 years] and older [55–65 years]). Younger females