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Understanding and Treating Alcohol Craving and Dependence: Recent Pharmacological and Neuroendocrinological Findings

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Abstract — There is a substantial need for discovering innovative ways to provide more information on the neurobiology of alcohol dependence as well as to discover more effective pharmacotherapies for alcohol dependence. Current research includes exploring new pathways able to modulate alcohol craving. In particular, research shows that several neuroendocrinological pathways may be involved in the neurobiology of alcohol craving and dependence. The first part of this review examines recent clinical findings on the role of feeding-related peptides in alcohol craving and dependence. Second, this review focuses on the need to discover new medications that may prove to be safe and effective in the treatment of alcohol dependence. For example, the GABAB receptor has been suggested as a new possible neuropharmacological target in the treatment of alcohol dependence. Accordingly, the second part of this review examines recent clinical findings on the role of the selective GABAB receptor agonist baclofen in the treatment of alcohol-dependent subjects. These two distinct topics will be both analyzed and discussed. The final part of this review discusses possible connections between these two topics, as an example of possible interactions between psychoneuroendocrinology and neuropharmacology. These possible interactions could lead to future intriguing research aimed at understanding and treating alcohol craving and dependence.

INTRODUCTION

Alcohol craving represents an important theoretical construct in the literature of alcohol dependence. Alcohol craving is generally defined as a strong urge to consume alcohol. It could be thought of as a phenomenon integrating a desire to increase a positive feeling and/or to overcome one that is negative. Craving can occur spontaneously, or it can be elicited by internal or external stimuli known as cues (see Swift, 1999). Internal cues may include emotional states (e.g. anxiety) or symptoms of acute alcohol withdrawal, whereas external cues may include exposure to alcohol-related environments or objects (e.g. bottles of alcoholic beverages or advertisements) (Swift, 1999).

The neurobiochemical mechanisms implicated in the etiology of craving involve several neurotransmitters, such as dopamine, gamma-aminobutyric acid (GABA), opioids, glutamate and serotonin (see McBride and Li, 1998; Weiss and Porrino, 2002; Addolorato et al., 2005a; Swift, 2007). The neurobiology of alcohol craving and dependence is extremely complex and not completely understood. Therefore, it is necessary to further elucidate the mechanisms at the basis of alcohol craving as well as the possible presence of factors able to modulate craving itself. It would be beneficial to better understand the mechanisms able to modulate alcohol craving in order to identify new neuropharmacological targets to treat alcohol dependence.

Some of the clinical research focused on understanding and treating alcohol craving and dependence may be categorized in two lines of research.

(1) Studies focused on the neurobiological mechanisms of alcohol craving: these include studies developing new laboratory paradigms to assess craving; validation of assessments able to quantify alcohol craving and identify specific craving pathways; genetic studies focused on specific polymorphisms associated with craving; and studies focused on the possible role of different neuroendocrine pathways in the neurobiology of alcohol craving. This review will focus on the role of neuroendocrinological pathways in alcohol craving and dependence.

(2) Studies focused on the neuropharmacology of alcohol craving: these include studies testing different drugs working on neurotransmitters like dopamine, opioids, serotonin, GABA and others. This review will focus on the role of the GABABergic medication baclofen as a treatment for alcohol craving and dependence.

The following review explores two distinct topics:

(1) clinical studies that focus on the role of specific neuroendocrine pathways (i.e. appetitive peptides) will serve as an example of research where the primary goal is to investigate new pathways that can influence the mechanisms of alcohol craving;
(2) clinical studies testing the role of the GABABergic baclofen in alcohol dependence will serve as an example of research where the primary goal is to investigate new medications that are potentially safe and effective in the treatment of alcohol dependence.

UNDERSTANDING AND TREATING ALCOHOL CRAVING AND DEPENDENCE: RECENT NEUROENDOCRINOLOGICAL FINDINGS

Evidence suggests that several neuroendocrine pathways may play a role in the mechanisms on the basis of alcohol craving and alcohol dependence. In particular, there is an increasing interest in the role of feeding-related pathways and their response in alcohol craving and dependence. In fact, research shows that...
alcohol and food-seeking behaviors share some common neural pathways (Li et al., 1987; Blum et al., 1996; Volkow et al., 2008; Addolorato et al., 2009). As a consequence, overlapping neuronal circuits exist between addiction and obesity (see Volkow et al., 2008). Therefore, neurobiological circuits related to the food-seeking behavior have been suggested as possible new targets in the treatment of alcohol dependence, such as the cannabinoid (CB; see Colombo et al., 2005) and the neuropeptide Y system (NPY; see Heilig and Thorsell, 2002). Consistent with these observations, there is converging research suggesting that feeding-regulating circuits may provide important information in understanding alcohol craving and dependence. These circuits involve peptides that are either orexinergic (e.g. ghrelin), anorexigenic (e.g. leptin, insulin, adiponectin) or both (e.g. thyroid hormones). These pathways are summarized in this review.

### Leptin

Leptin is a neuropeptide secreted by white adipocytes. Leptin acts as a key regulator of food intake and energy expenditure, which plays an important role in hypothalamic appetite regulation (Inui, 1999). Leptin also regulates the hypothalamic–pituitary–adrenal (HPA) axis, which is involved in the neurobiology of alcohol craving (Adinoff et al., 2005; Addolorato et al., 2005a).

Both animal and clinical studies point toward a pathophysiological role of leptin in the neurobiology of alcohol craving. For example, leptin may enhance motivation for alcohol consumption in habituated mice after alcohol withdrawal (Kiefer et al., 2001a). Similarly, in alcohol-dependent subjects, plasma leptin is significantly higher than that in healthy controls, and it correlates with self-rated craving and decreases during withdrawal (Kiefer et al., 2001b). Furthermore, Kiefer et al. (2005) found an association between leptin plasma levels and relapse. In the same study, leptin levels decreased significantly in patients undergoing pharmacological treatment with naltrexone and acamprosate.

Other research demonstrated an association of leptin with alcohol craving during withdrawal in female patients (Kraus et al., 2004). Notably, this study used the Obsessive Compulsive Drinking Scale (OCDS) to assess craving, while the Visual Analogue Scale (VAS) was used in the Kiefer et al.’s studies. In a larger study looking at 189 male and female alcohol-dependent patients, both genders showed a positive correlation between leptin serum levels and alcohol OCDS craving (OCDS) (Hillemacher et al., 2007a). It should be noted that other studies were focused on the relationship between leptin and nutritional parameters and they did not find short-term changes of leptin levels in alcohol-dependent subjects (e.g. Santolari et al., 2003).

Altogether, these results suggest that the role of leptin in alcohol dependence might be of more importance in some specific subgroups of individuals. Consistent with this consideration, Hillemacher et al. (2007b) performed a re-analysis of their previous results (Hillemacher et al., 2007a) classifying the subjects according to the Lesch typologies (Lesch et al., 1990). Results showed that leptin levels were highest in Type 4 patients and lowest in Type 1 patients. Furthermore, leptin serum levels were positively associated with craving particularly in patients of Lesch’s Type 1 and 2, and not in patients of Types 3 and 4 (Hillemacher et al., 2007b). Finally, it is also noteworthy that in these studies (Kraus et al., 2004; Hillemacher et al., 2007a, 2007b), the authors analyzed the leptin/body mass index (BMI) ratio that is probably a more accurate index than leptin alone because leptin secretion is proportional to fat mass.

In summary, the available studies suggest a pathophysiological role of leptin in alcohol craving, possibly mediated via its impact on the HPA axis (Hillemacher et al., 2007a).

### Adiponectin

Similar to leptin, adiponectin represents a neuropeptide secreted by white adipocytes and involved in hypothalamic appetite regulation (Ahima, 2004; Qi et al., 2004). A recent study investigated the blood adiponectin level in alcohol-dependent patients. These patients showed a significant decrease of adiponectin during the course of withdrawal (Hillemacher et al., 2009a). Furthermore, the adiponectin level showed a significant negative correlation with self-rated craving, but only in male subjects. In summary, adiponectin could be involved in the neurobiology of alcohol craving, possibly via its effects on the hypothalamic circuits (Hillemacher et al., 2009a).

### Ghrelin

Ghrelin is a 28-amino-acid peptide acting as the endogenous ligand for the growth hormone secretagogue (GHS) receptor (Kojima et al., 1999). Ghrelin was first discovered as a peptide produced by the stomach (Kojima et al., 1999). Furthermore, research showed a central hypothalamic production of ghrelin (Nakazato et al., 2001).

Recent preclinical studies demonstrate that ghrelin centrally administered into the ventral tegmental area (VTA) increases extracellular concentrations of accumbal dopamine (Jerlhag et al., 2007), and both ghrelin and ethanol activate the cholinergic–dopaminergic reward link, implying neurochemical analogies between ghrelin and ethanol (Jerlhag et al., 2007, 2008). Similar results were found when ghrelin was injected peripherically (Jerlhag, 2008). Ghrelin’s administration into the lateral hypothalamus or paraventricular nucleus had no effects on ethanol consumption (Schneider et al., 2007). This suggests that ghrelin works in specific brain reward nodes such as VTA (Jerlhag et al., 2008).

Altered ghrelin levels have been shown in both healthy controls after alcohol exposure and in alcohol-dependent individuals. In particular, Calissendorff et al. (2005) demonstrated that alcohol, compared to water, significantly reduced ghrelin levels. Zimmermann et al. (2007) also demonstrated a significant reduction in plasma ghrelin levels after alcohol ingestion in healthy controls but unchanged ghrelin levels after a laboratory stressor exposure. Clinical studies tested ghrelin levels in alcohol-dependent subjects compared to healthy controls. These studies showed lower ghrelin levels in actively drinking alcohol-dependent patients (Addolorato et al., 2006a; Badouei et al., 2008) and a significant increase of ghrelin levels during abstinence (Kim et al., 2005; Kraus et al., 2005).

Using the Visual Analogue Scale (VAS) and the OCDS, no correlation between ghrelin and craving was found by Kraus and colleagues (2005). On the contrary, we tested actively drinking alcohol-dependent subjects and found a significant positive correlation between ghrelin and the total OCDS score. Also, there was a trend toward a significant correlation between ghrelin and the compulsive OCDS (CP) score.
(Addolorato et al., 2006a). However, no correlation between ghrelin and the obsessive OCDS (OB) score was found (Addolorato et al., 2006a).

Several factors could explain the discrepancy between these two studies, including differences related to patients’ typologies, gender and genotype(s). For example, reanalysis of the study by Kraus et al. (2005) was conducted by the same lab applying the Lesch typology classification (Lesch et al., 1990). This analysis showed a trend toward a negative correlation between ghrelin and the OCDS score but only in a subgroup (Lesch’s 1 typology) of alcohol-dependent patients (Hillemacher et al., 2007b), whereas, Wurst et al. (2007) found a positive relationship between ghrelin levels and the CP subscore in female alcohol-dependent subjects. Finally, a recent study involving 417 individuals (abstainers, moderate and heavy alcohol drinkers) performed a haplotype analysis of the pro-ghrelin and GHS-R genes, demonstrating an association between the single nucleotide polymorphism (SNP) rs2232165 of the GHS-R gene and heavy alcohol use (Landgren et al., 2008).

In summary, these animal and human investigations suggest that the ghrelin system could play a role in the neurobiology of alcohol dependence. This is consistent with the growing evidence that elevated ghrelin levels may contribute to cravings for food, stimulant drugs or alcohol (Cummings et al., 2007). Altogether, these results suggest that the ghrelin system deserves future investigations in the field of alcohol dependence.

**Insulin**

Insulin is secreted by the pancreatic (β)-cells together with the C-peptide and is involved in the regulation of glucose homeostasis. Interestingly, some preclinical studies suggest a role of insulin in some neurobiological pathways on the basis of addiction. For example, in mammals, insulin modulates food rewards and increases food intake, acting directly at the VTA and indirectly through the hypothalamus (Figlewicz, 2003). Moreover, the dopamine transporter (DAT) mRNA of the VTA increases in rats treated with intraventricular insulin (Pristupa et al., 1994). In Drosophila, a role of the insulin/insulin-receptor pathway in regulating behavioral responses to alcohol has been suggested (Corl et al., 2005). On the basis of this preclinical evidence, we performed a set of three consecutive experiments (retrospective, case-control and longitudinal) in order to investigate the relationship between blood insulin and alcohol craving in alcohol-dependent individuals. The results showed a significant positive correlation between the blood insulin level and the OCDS craving (Leggio et al., 2008a). Moreover, insulin was strongly related to the compulsive OCDS subscore, while a trend of correlation with the obsessive OCDS subscore was found. There was a significant correlation between insulin and craving in our alcohol-dependent patients during the active drinking phase. After 12 weeks of total abstinence, this correlation disappeared, suggesting that the link between insulin and craving was only during the active drinking phase (Leggio et al., 2008a).

The link between insulin and the dopaminergic system (in particular with the DAT) could represent a possible neurobiological explanation of these findings. During the 12 weeks of abstinence, the patients were treated with baclofen (details about baclofen are described below). Baclofen reduces dopamine release via the GABAB system. Therefore, either alcohol abstinence or baclofen (or both) could explain why the correlation between insulin and craving disappeared after a period of abstinence.

In these experiments, we also tested blood C-peptide and insulin growth factor-1 (IGF-1) levels. No correlation between alcohol craving and IGF-1 was found during the active drinking phase or after 12 weeks of abstinence. On the contrary, C-peptide showed significant correlations with alcohol craving, similar to those described for insulin (Leggio et al., 2008a). C-peptide is a peptide cleaved-off during the synthesis of insulin while IGF-1 is produced by the liver. Therefore, these results confirm that the link with alcohol craving was specific of insulin but not of other growth factors with a structure similar to insulin.

**Thyroid hormones**

A role of thyroid hormones in regulating appetite is well recognized, with higher levels of thyroid hormones inducing a higher appetite (Pijl et al., 2001). Furthermore, an involvement of the hypothalamic–pituitary–thyroid (HPT) axis has been recognized in alcohol-dependent patients (for an extensive review, see Hermann et al., 2002). For example, several studies have shown a reduction in peripheral thyroid hormone and/or blunted thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) in alcohol dependence (Valimaki et al., 1984; Baumgartner et al., 1994; Garbutt et al., 1996). Moreover, it has been demonstrated that TSH is modulated by dopamine (Cooper et al., 1983) in the hypothalamus and/or the pituitary gland (Delitala et al., 1981).

Recently, we have studied the relationship between thyroid hormones and craving in alcohol-dependent subjects. Applying the same design used to investigate the relationship between alcohol craving and insulin (Leggio et al., 2008a), we studied TSH, free-T3 and free-T4 during the active drinking phase and after 12 weeks of total abstinence (Leggio et al., 2008b). During the 12 weeks, subjects were treated with baclofen. The results of this study demonstrated that during the active drinking phase, there was a significant inverse correlation between TSH and craving. This was measured using the OCDS score, the OB subscore, the CP subscore and the Penn Alcohol Craving Scale (PACS) (Leggio et al., 2008b). Furthermore, TSH showed an inverse significant correlation with assessments measuring state anxiety (State Inventory test; STAI-Y1), trait anxiety (Trait Inventory test; STAI-Y2), current depression (Zung Self-Rating Depression Scale; Zung-SDS) and aggressiveness (Aggressiveness Questionnaire; AQ). All of these significant correlations disappeared after 12 weeks of abstinence. Moreover, at baseline and after 12 weeks of abstinence, we found a significant direct correlation between the free-T3 and both the OCDS score and the CP subscore (Leggio et al., 2008b).

Together, these results suggest a possible role of the HPT axis in alcohol craving. Consistent with this hypothesis, it has been demonstrated that TSH is modulated by dopamine (Delitala et al., 1981; Cooper et al., 1983) and that alcohol craving is inversely correlated with dopamine D2 receptors’ availability (Heinz et al., 2004). These results lead us to speculate that TSH could influence alcohol craving by a depressive or anxious mood (see Fig. 1). Furthermore, lower TSH levels could facilitate the increase in both current depression and anxiety. Current depression and anxiety could then facilitate alcohol craving (Leggio et al., 2008b).
Volume-regulating and stress-related hormones

The findings presented in the previous section of this review present some common features; in particular (i) feeding-related peptides have a strong relationship with the compulsive component of alcohol craving (i.e. ghrelin, insulin, free-T3), and (ii) feeding-related peptides are correlated with alcohol craving during the active drinking phase but not during a period of total alcohol abstinence (i.e. ghrelin, insulin, TSH). Therefore, we based our research on whether these findings were unique of appetitive peptides. Particularly, we wanted to test the link between alcohol craving and other HP-hormones that are not directly involved in the control of appetite (volume-regulating and stress-related hormones).

Volume-regulating hormones. Volume-regulating hormones, such as renin, aldosterone, vasopressin and natriuretic peptides, could play a role in alcohol dependence (Kovacs, 2000). For example, animal studies show that rats with the double dose of the S-allele renin gene drink significantly more alcohol than those that receive a single dose (O’Dowd and Grupp, 1991). In alcohol-prefering rats, alcohol preference could be related to an increased vasopressin gene expression in the paraventricular nucleus (Hwang et al., 1998). Consistent with this preclinical evidence, studies have also shown that in alcohol-dependent patients, there has been increased plasma renin activity and aldosterone during alcohol withdrawal and their normalization during recovery (Kovacs, 2000). Moreover, significant alterations of both plasma levels (Kiefer et al., 2002; Doring et al., 2003) and precursor genes of the atrial natriuretic peptide (ANP) (Hillemacher et al., 2009b) in alcohol-dependent subjects were suggested. Furthermore, Hillemacher et al. (2006) demonstrated that daily alcohol volume intake directly correlates with craving in alcohol-dependent patients.

We tested renin, aldosterone and the N-terminal pro B-type natriuretic peptide (NT-proBNP) in our alcohol-dependent subjects during their active drinking phase and after 12 weeks of abstinence (Leggio et al., 2008c). At 12 weeks, we observed a significant increase of renin and a significant decrease of aldosterone. At baseline, no correlations between the hormones tested and craving scores were found. At 12 weeks, aldosterone showed a significant direct correlation with the OB subscore and with the trait anxiety scores (STAI-Y2). Renin demonstrated a significant direct correlation with the OB subscore and with the PACS score. The NT-proBNP never correlated with craving measurements.

Our results suggest that the renin–aldosterone axis could play a role in alcohol craving in medium-term abstinent patients and thereby leading to the hypothesis that alcohol craving could be influenced by the fluid volume intake. In particular, the
relationship between some volume-regulating hormones and alcohol craving, only in the abstinence phase of our patients, could be related to some changes in salt and fluid volume homeostasis, e.g. the dehydration resulting from acute alcohol ingestion (Di Gennaro et al., 2002) and the excessive thirst and fluid intake displayed by abstinent alcohol-dependent individuals (Doring et al., 2003).

Stress-related hormones. A role of the HPA axis in alcohol dependence is well recognized (Adinoff et al., 2005; Morrow et al., 2006; Clarke et al., 2008). For example, an ethanol-induced HPA axis injury in actively drinking alcoholics (Wand and Dobs, 1991) and an impaired hypothalamic and pituitary responsiveness in recently withdrawn chronic alcoholics (Costa et al., 1996) have been described. Furthermore, it has been shown how a relatively high dose of alcohol taken orally is able to produce an increase of cortisol that is smaller in heavy drinkers compared to light drinkers (King et al., 2006). Ultimately, it has been suggested that neurosteroids may have therapeutic use in alcohol withdrawal or for relapse prevention (Morrow et al., 2006).

After 12 weeks of abstinence in our alcohol-dependent subjects, the adrenocorticotropic hormone (ACTH) and cortisol showed a significant decrease of blood cortisol (but not ACTH) levels. However, during the active drinking phase and after 12 weeks of abstinence, we did not find any significant correlation between cortisol/ACTH and alcohol craving (Leggio et al., 2008b). The lack of a significant association between cortisol levels and self-reported craving for alcohol is contrary to the previous findings by O’Malley et al. (2002). This feature could be related, at least partially, to the different population and study design. In fact, O’Malley et al. (2002) performed a self-administration alcohol laboratory study with a population of non-treatment-seeking alcohol-dependent subjects. Conversely, our results are consistent with several studies that did not find support for an association between alcohol craving and cortisol levels in treatment-seeking alcohol-dependent individuals (Kiefer et al., 2006). Furthermore, there was no association in laboratory studies testing cortisol in non-treatment-seeking alcohol-dependent subjects during a cue-reactivity experiment (Ooteman et al., 2007) or in hazardous drinkers during an intravenous alcohol infusion (Ray et al., 2009).

On the other hand, we found a significant inverse correlation between cortisol and fat mass during the active drinking phase but not after 12 weeks of abstinence (Leggio et al., 2009a). This feature is consistent with the hypothesis that the HPA axis plays a role in the nutritional impairment present in alcoholic subjects (Addolorato et al., 1998).

Conclusions: Are feeding-related peptides new possible targets in the treatment of alcohol dependence?

Our primary goal was to identify the link between alcohol craving and feeding-related peptides. Therefore, our experiments included feeding-related peptides as well as other groups of HP-related hormones that are not directly related to the control of appetite. Our experiments had some limitations, such as a small sample size, the absence of several repeated hormone measures and the lack of a placebo arm. In fact, in all experiments, the design was open label and all subjects were treated with baclofen. Therefore, the decreased cortisol and aldosterone levels during abstinence could be primarily related to reduced stress, as seen in the reduction of the anxiety scores. These results could also be related to the anxiolytic properties of baclofen (Krupitsky et al., 1993; Addolorato et al., 2002a; Flannery et al., 2004). Despite these limitations, the results could potentially lead to more sophisticated studies.

The overall results of our experiments suggest that during the active drinking phase but not after a period of total abstinence, feeding-related peptides are linked to alcohol craving and, in particular, to the compulsive component of alcohol craving.

The presence of a correlation between feeding-related peptides and alcohol craving only during the active drinking phase suggests that feeding-related peptides could be related only to ‘acute’ craving, in other words the ‘urge to drink’. Accordingly, in the last set of experiments that tested the HPT axis, we measured craving not only with the OCDS scale but also with the PACS. Notably, we found that TSH correlated not only with the OCDS but also with the PACS score. The PACS reflects the ‘appetitive urge’ to drink (Flannery et al., 2003).

The presence of a strong correlation between feeding-related peptides and the compulsive craving subscore is consistent with the observation that compulsion reflects the behavioral reward mechanisms characterizing addictive disorders, such as eating disorders (Cassin and von Ranson, 2005). In other words, this observation is consistent with the well-recognized notion that alcohol- and food-seeking behaviors share some common neural pathways.

We observed that the volume-regulating hormones correlated with alcohol craving but the relationship was completely opposite to that of feeding-related peptides. In fact, renin and aldosterone correlated only with the OB score and only after a period of abstinence. These different relationships lead to hypothesize that different groups of hormones (volume-regulating versus feeding-related hormones) could influence different neurobiological pathways (respectively, obsessive versus compulsive craving) and could reflect the overlap between alcohol-seeking behavior and different appetite pathways (respectively, salt versus sweet appetite) (Leggio et al., 2008c).

Our data are consistent with other data showing the lack of an association between cortisol and alcohol craving. This observation further supports our hypothesis that the relationship between feeding-related peptides and alcohol craving reflects a specific role of appetitive pathways in the compulsive alcohol-seeking behavior. Moreover, we also note that the lack of an association between cortisol and alcohol craving does not contrast with the well-known involvement of the HPA axis in alcohol dependence, especially in alcohol sensitivity and drinking (Morrow et al., 2006). In fact, the available literature leads to conclude that the role of the HPA axis in alcohol drinking is not mediated by a possible influence on alcohol craving. This concept is also consistent with the notion that craving is not always associated with alcohol drinking (Swift, 1999).

The correlations between alcohol craving and feeding-related peptides were positive correlations in the case of ghrelin, leptin, insulin and IT3 and negative correlations in the case of adiponectin and TSH. These different kinds of correlations are consistent with the different actions of these hormones. However, these feeding-related peptides also share some similar biochemical mechanisms. For example, all these feeding-related peptides are able to modulate glucose homeostasis. Alcohol is able to acutely modify blood glucose levels (Swift and Davidson, 1998; Vonghia et al., 2008). However, interestingly
enough glucose metabolism plays a role in the alcohol preference and seeking behavior. For example, Connelly et al. (1983) demonstrated that the hyperglycemic C57BL mice show a preference for ethanol and when given oral antidiabetic drugs, it lowered their blood glucose levels as well as decreased their desire for ethanol. Similarly, the Wistar rats that are glucose intolerant had shown a preference for ethanol and consumed approximately three times more ethanol than control animals (Zito et al., 1984). In humans, Blum et al. (2007) developed a model named ‘Reward deficiency syndrome’ (RDS), which suggested that subjects with an addiction disorder (i.e. alcohol dependence, binge eating) have genetic alterations of the dopamine brain system and that the dopamine–glucose link plays a key role in the RDS. Blum and colleagues (2007) hypothesized that this ‘deficiency’ drives individuals to engage in activities of behavioral excess, which will increase brain dopamine function. Interestingly, a secondary analysis of the large COMBINE sample (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) Study (Anton et al., 2006)) suggested that in alcohol-dependent individuals, the blood glucose level might predict and influence the alcohol use behavior and the related alcohol consumption (Leggio et al., 2009b).

Research aimed at identifying mechanisms able to manipulate glucose metabolism (i.e. feeding-related peptides) could offer new approaches in the treatment of alcohol dependence. Therefore, research on feeding-related peptides, linked to alcohol craving and dependence, could identify new possible targets in the treatment of alcohol-dependent subjects (see Fig. 2). For example, the ghrelin system represents an interesting pathway. Several animal and human studies that are reported in this paper demonstrated the similarities between ghrelin and alcohol and the possible involvement of ghrelin in the alcohol-seeking behavior. We also noted some discrepancies amongst these studies. The discrepancies, however, were partially clarified by applying a typology classification, namely the Lesch typology classification (for an extensive review on

![Fig. 2. The figure outlines a possible hypothetical model how hormones, and in particular feeding-related peptides, might be linked to several characteristics of alcohol dependence, such as compulsive craving, obsessive craving, alcohol drinking, alcohol abstinence and relapse.](image_url)

The need to further explore the mechanisms at the basis of alcohol craving and dependence could ultimately lead to identify pharmacological targets that would help clinicians in the management of their alcohol-dependent subjects. In particular, a general assumption is that medications that reduce craving may be effective in the treatment of alcohol dependence. In the last decades, several medications have been tested for the treatment of alcohol-dependent individuals with the goal to improve the effectiveness of alcoholism treatments (Litten et al., 1996; Addolorato et al., 2005b; Swift and Leggio, 2009). As a consequence, pharmacotherapy for alcohol dependence is undergoing a period of growth and scientific excitement. Several drugs have shown efficacy to reduce alcohol craving and consequently increase abstinence and prevent alcohol relapse (see Addolorato et al., 2005b; Swift, 2007). Among them, disulfiram, oral and injectable (long acting) naltrexone, and acamprosate have been approved for alcohol dependence (see Swift, 2007; Garbutt, 2009). However, the general perception is that their overall efficacy is modest, despite the fact that some patients largely benefit from these medications.

Therefore, there is the need to identify new neurobiological pathways that can serve as possible targets in treating alcohol-dependent individuals (see Heilig and Egli, 2006). Among these new possible neuropharmacological targets, there is an increasing interest in studying medications working on the GABA system (Johnson et al., 2005). Consistent with this trend, we have investigated the anti-alcohol properties of the GABA receptor agonist, baclofen.

Baclofen, approved by the Food and Drug Administration (FDA) for the treatment of spasticity (Fig. 3), is a selective GABA<sub>B</sub> receptor agonist. At a preclinical level, baclofen has been intensively studied in a model of excessive alcohol consumption, namely the Sardinian alcohol-prefering (sP) rats (Colombo, 1997; Colombo et al., 2006). These studies, when tested under the homecage (two-bottle ‘alcohol versus water’
choice regimen), demonstrated that the repeated administration of non-sedative doses of baclofen, dose-dependently, suppresses the acquisition and maintenance of the alcohol drinking behavior in sP rats. Moreover, acute injection of baclofen completely blocked the temporary increase in voluntary alcohol intake occurring after a period of abstinence. Acute treatment with baclofen also dose-dependently suppressed extinction responding for alcohol in sP rats trained to lever-press for oral alcohol self-administration (for an extensive review of animal studies testing baclofen in alcohol dependence, see Colombo et al., 2004).

Although these results have been found in some animal models but not others, the overall significance of these studies is that there is an involvement of the GABAA receptor in the neural substrate mediating alcohol intake and alcohol motivational properties.

Role of baclofen in reducing alcohol craving and intake, promoting alcohol abstinence

A first pilot open-label study performed in alcohol-dependent patients showed that baclofen administered orally (30 mg/day after a 3-day titration) reduced alcohol craving and intake (Addolorato et al., 2004). In 2004, this study was repeated by Flannery et al. (2004) and showed similar results. In particular, Flannery et al. (2004) reported a significant reduction in the number of drinks per drinking day and the number of heavy drinking days. Also, a significant decrease in anxiety and craving was reported (Flannery et al., 2004).

The efficacy of baclofen was also evaluated in a double-blind randomized controlled study, where 39 alcohol-dependent patients were enrolled (Addolorato et al., 2002a). This study indicated that the percentage of dropouts was lower in the baclofen group with respect to the placebo group, and a significantly higher percentage of patients achieving and maintaining abstinence throughout the experimental period were found in the baclofen group compared with subjects treated with placebo. Baclofen was effective in reducing daily alcohol intake within the first week of treatment. In patients who continued to drink, baclofen continued to be effective in reducing daily alcohol consumption. Cumulative abstinence duration (CAD) was significantly higher in baclofen- than that in placebo-treated patients. Baclofen was shown to be significantly effective in reducing the OCDS total score and both compulsive and obsessive components of OCDS were also found.

Notably, both the double-blind study by Addolorato et al. (2002a) and the open-label study by Flannery et al. (2004) showed a reduction of anxiety in baclofen-treated alcohol-dependent subjects. These observations are consistent with a previous study demonstrating that baclofen was effective in reducing anxiety in alcoholic patients, with an efficacy superior to placebo and equal to diazepam (Krupitsky et al., 1993). Moreover, the anxiolytic effect of baclofen is consistent with the role of the GABAA receptor in modulating the anxious behavior (Cryan and Kaupmann, 2005).

Recently, we performed a larger randomized controlled trial enrolling alcohol-dependent patients affected by cirrhosis. The rationale to perform this study was based on the following concepts: (i) total alcohol abstinence represents the most effective strategy for alcoholic patients affected by a liver disease; (ii) cirrhotic patients are usually excluded from trials investigating anti-craving drugs because of a concern that these medications might worsen liver disease; and (iii) baclofen has very low levels of liver metabolism (about 15%), which is mainly eliminated unmodified by kidney, and no hepatic side effects have been reported either in alcoholic patients or in patients with neurological disorders treated with baclofen.

All patients enrolled in the study were diagnosed with both alcohol dependence and liver cirrhosis. Eighty-four patients were randomized to receive baclofen (10 mg t.i.d.) or placebo for 12 consecutive weeks (Addolorato et al., 2007). At each visit, routine psychological support counseling was provided by the same trained professional staff and attendance at other support groups (e.g. Alcoholics Anonymous) was strongly encouraged. Results of this trial showed a significantly higher number of patients who achieved and maintained abstinence throughout the experimental period in the baclofen group compared to the placebo group. CAD was approximately two-fold higher in baclofen- than that in placebo-treated patients. Moreover, a significant effect of baclofen compared to placebo was found in reducing the OCDS total score and its subscores. Furthermore, treatment with baclofen significantly reduced several liver parameters (i.e. alanine aminotransferase, gamma-glutamyl transferase, bilirubin and international normalized ratio) and significantly increased albumin values (Addolorato et al., 2007). No important adverse events (including hepatic side effects) were reported.

Several pharmacological treatments may be used in the treatment of alcoholic cirrhosis (see Haber et al., 2003). However, meta-analytic studies have shown that even low doses of daily alcohol intake are associated with an increased risk of cirrhosis (Corrao et al., 2004). Oxidative mechanisms are activated even at low doses of alcohol consumption (Addolorato et al., 2008; Leggio and Addolorato, 2009) and play a key role in alcohol-related impairment and damage (see Albano, 2008). In particular, inflammatory and immune responses along with oxidative stress and alterations in adipokine secretion may contribute in different ways to the evolution of alcohol-induced liver damage until reaching the condition of fibrosis/cirrhosis (see Lieber, 1997, 2004; Albano, 2008; Vidali et al., 2008). Furthermore, continuing alcohol abuse is a risk factor for cirrhosis-related complications, including hepatocellular carcinoma (Tilg and Day, 2007). Therefore, total alcohol abstinence represents the cornerstone in treating alcoholic patients affected by cirrhosis (see Tilg and Day, 2007). Consequently, achieving total alcohol abstinence is imperative in the treatment of patients affected by any stage of liver cirrhosis (Tilg and Day, 2007). Consistent with this aim, our study represents a potentially important result in public health. This study underlines the importance to transfer clinical research findings to the primary care settings and opens the way for
Role of baclofen in reducing alcohol withdrawal symptoms

Symptoms of alcohol withdrawal syndrome (AWS) usually develop within 6–24 h of the last drink and include—in light to moderate forms—the presence of raised blood pressure and pulse rate, tremor, hyperreflexia, irritability, anxiety and depression (see Hall and Zador, 1997). The main objectives of the clinical management of AWS are to minimize the severity of symptoms, prevent the occurrence of more severe withdrawal manifestations, such as seizures and delirium tremens (DT), and facilitate admission of the patient into a treatment program in an attempt to achieve and maintain long-term abstinence from alcohol (see O’Connor and Schotternfeld, 1998). Benzodiazepines represent the drugs of choice in the treatment of AWS (for a meta-analytic review, see Mayo-Smith, 1997). Benzodiazepines may have negative side effects and addictive properties. Therefore, the discovery of potentially useful and manageable drugs for the treatment of AWS is critical. In particular, several GABAergic medications, including baclofen, have been tested and have shown no addictive properties or side effects (see Leggio et al., 2008d).

The first open-label clinical study showed how baclofen (10 mg orally administered every 8 h) rapidly suppressed symptoms of severe AWS (Addolorato et al., 2002b). A rapid decrease of the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) score and a marked improvement in AWS symptoms were observed shortly after baclofen administration in all patients. Furthermore, it was reported that a case of severe AWS complicated by DT was successfully treated with baclofen (Addolorato et al., 2003). AWS and DT symptoms were rapidly suppressed by the oral administration of baclofen 25 mg every 8 h for the first 3 days, subsequently tapering the dose to 10 mg every 8 h. More recently, we have compared the efficacy of baclofen in treating AWS with the ‘gold standard’ diazepam. In a comparative randomized study, we enrolled 37 alcohol-dependent patients with moderate to severe AWS (Addolorato et al., 2006b). Subjects were randomized to receive baclofen (30 mg/day for 10 consecutive days) or diazepam (0.5–0.75 mg/kg/day for six consecutive days, tapering the dose by 25% daily from Day 7 to Day 10). There was a significant decrease in the total CIWA-Ar score in both groups without any significant difference between the two groups. Similarly, there was a significant decrease of the CIWA-Ar subscores for sweating, tremors, anxiety and agitation in both groups, with no significant differences between the two treatments. In summary, this study showed that baclofen was able to reduce AWS-related symptoms in a manner comparable to the ‘gold standard’ diazepam (Addolorato et al., 2006b). Finally, in a retrospective chart review, the efficacy of baclofen in the preventive treatment of alcohol withdrawal reported an 86% success rate (Stallings and Schrader, 2007). Notably, the role of baclofen in reducing alcohol withdrawal in humans (Addolorato et al., 2002b, 2006b) is consistent with some animal experiments where baclofen was active against both stress sensitization of a future withdrawal and the acute consequences of stress during abstinence after a history of repeated withdrawals (Knapp et al., 2007).

Manageability and safety of baclofen in the treatment of alcoholic individuals

Baclofen has been administered for many years as a particularly manageable and safe antispasticity drug (Davidoff, 1985). Similarly, our studies demonstrated that baclofen was safe and manageable when administered in alcohol-dependent subjects. Furthermore, few side effects were reported without any serious adverse events. Of importance, baclofen showed an excellent hepatic safe profile with the lack of liver-related side effects in alcohol-dependent subjects both with and without liver cirrhosis.

During our studies, we noted that patients who continued to drink alcohol while being treated with baclofen showed no signs of any complications. A recent laboratory study confirmed these findings by administering baclofen (0 mg, 40 mg or 80 mg) simultaneously with alcohol in non-treatment-seeking heavy social drinkers using a double-blind double-dummy design (Evans and Bisaga, 2009).

Finally, no patient treated with baclofen reported either drug-induced euphoria or other pleasurable effects or any degree of craving for the drug. When baclofen was discontinued, no drug withdrawal syndrome and/or side effects due to drug suspension were observed. The absence of additive properties of baclofen represents a feature of paramount importance for the pharmacological treatment of alcohol-addicted patients.

Conclusions: Baclofen—a new drug for the treatment of alcohol dependence?

Baclofen demonstrated efficacy in reducing alcohol craving and intake, therefore promoting abstinence as well as relieving alcohol withdrawal symptoms. This feature is of interest since it suggests that baclofen may represent a unique pharmacotherapy for use in the treatment of alcohol dependence (Addolorato et al., 2006c).

However, further work is needed to better understand how baclofen may be used in treating alcohol-dependent individuals. One recent US trial confirmed the safety of baclofen in alcohol-dependent subjects but, however, failed to show the effect of baclofen in either heavy drinking days or abstinent days (Garbutt et al., 2007). It is suggested that the differences in patient populations and recruitment methods in the European versus US trials may have contributed to the differences in outcomes (Garbutt, 2009). Therefore, future studies will need to specify which alcohol-dependent subjects may better respond to baclofen administration.

For example, considering the role of baclofen in reducing both alcohol craving and anxiety, the role of baclofen in alcohol-dependent subjects with anxiety comorbidity will have to be addressed. This concept is also supported by our studies testing hormones and peptides in alcohol dependence (described in the previous section). In fact, baclofen-treated AD individuals demonstrated a reduction of craving and anxiety as well as of HPA-related hormones such as aldosterone and cortisol. Placebo-controlled studies, however, are needed to better address the role of baclofen in modulating the HPA axis and other neuroendocrine pathways.

Another aspect to be addressed will be the use of higher doses of baclofen. Both the European and the US trials used baclofen at the dose of 30 mg/daily. Baclofen, however, is safely used at higher doses in clinical practice as a drug to control spasticity.
Moreover, the alcohol laboratory study performed by Evans and Bisaga (2009) points out the safety of baclofen up to 80 mg when acutely administered together with alcohol. Finally, two recent case reports have shown that the administration of higher doses of baclofen (up to 270 mg) was able to completely suppress alcohol craving and anxiety (Ameisen, 2005; Bucknam, 2007). Although anecdotal in nature, those reports further support the possibility of exploring higher doses of baclofen in the treatment of alcohol dependence.

Evans and Bisaga (2009) performed a laboratory study enrolling heavy drinkers without a diagnosis of alcohol dependence, therefore providing important information in terms of safety but less definitive results regarding the mechanisms how baclofen works (i.e. baseline or elicited alcohol craving). Therefore, future alcohol laboratory studies enrolling subjects with a diagnosis of alcohol dependence might better clarify the mechanisms how baclofen may modulate alcohol drinking and craving. Finally, the application of alcoholic subtypes’ classifications (see Leggio et al., 2009c) could potentially identify specific alcohol-dependent typologies better responding to baclofen administration.

In summary, despite the need of further studies, baclofen represents a promising medication in the treatment of alcohol-dependent subjects.

CONCLUSIONS

The first part of this review described the role of several and different neuroendocrine pathways, with an emphasis on the role of feeding-related peptides. Then, the second part of the review described the role of baclofen as a pharmacological treatment of alcohol dependence. Although this paper was divided into two distinct sections, the entire data summarized several important concepts and provided an example of possible interactions and connections between neuroendocrine and neuropharmacological pathways.

In particular, investigations on the role of feeding-related peptides could provide different information and approaches. A pioneeristic approach is to try to identify neuroendocrine pathways that could act as direct targets in the treatment of alcohol dependence. This aspect has already been discussed before (see ‘Conclusions: Are feeding-related...’ section). Another approach would be to use neuroendocrinological markers, such as appetite peptides, to better understand how some medications work. For example, it is interesting to test different groups of hormones in alcohol-dependent patients treated with baclofen and see if and how there hormones change during the treatment. This approach is of interest considering that some of the studies testing baclofen in alcohol dependence have provided conflicting results.

Therefore, the use of neuroendocrinological markers could be an intriguing approach that may provide us with more information on the mechanisms of how baclofen works. For example, animal and human studies have demonstrated the ability of baclofen in reducing anxiety in alcohol dependence. Animal studies show that baclofen blocks expression and sensitization of the anxiety-like behavior in a model of repeated stress and ethanol withdrawal (Knapp et al., 2007). Human studies show the ability of baclofen to reduce anxiety (Krupitsky et al., 1993), to reduce anxiety and craving (Addolorato et al., 2002a; Flannery et al., 2004; Leggio et al., 2008b) and to reduce AWS-related anxiety (Addolorato et al., 2006b). These observations suggest that baclofen may primarily affect relief-type craving (Addolorato et al., 2005b; Heilig and Egli, 2006) and theoretically, baclofen might work better in those alcohol-dependent patients with higher anxiety levels.

In the studies reported above (see ‘Understanding and treating alcohol...’ section), we determined hormone levels in alcohol-dependent patients before and after treatment with baclofen. Our preliminary results are consistent with the hypothesis that baclofen may primarily affect relief-type craving and work better in those alcoholics with anxiety. In fact, while feeding-related peptides have been related to the dopaminergic system, HPA-axis hormones (i.e. cortisol) and corticoid hormones (i.e. aldosterone) are more related to the stress/anxiety circuits. We would expect, therefore, that baclofen reduces stress/anxiety hormones but not feeding-related hormones. Consistent with this hypothesis, we found a significant reduction of aldosterone and cortisol as well as a significant reduction of craving and anxiety in alcohol-dependent patients treated with baclofen. On the contrary, there was not a significant decrease in feeding-related peptides after treatment with baclofen. Specifically, there were no changes in the thyroid hormones. Insulin even increased, a feature probably related to the changes in the body composition (see Leggio et al., 2008a). These observations confirm the utility of using neuroendocrinological markers in trials testing medications for alcohol dependence. Finally, we also note that this approach is consistent with other studies investigating the link between neuropharmacology and neuroendocrinology (i.e. the role of the HPA axis in naltrexone-treated alcohol-dependent subjects; see for example Kiefer et al., 2006).

More research is needed to understand if this integrative approach may lead to identifying connections between specific anti-craving medications (e.g. drugs targeting relief-type craving versus those targeting reward-type craving) and specific neuroendocrinological pathways (e.g. respectively, stress-related peptides versus appetite peptides). Furthermore, as already stated (see ‘Conclusions: Are feeding-related...’ section), more research is needed to understand if these neuroendocrinological pathways may serve per se as targets in the treatment of alcohol dependence.

Finally, recent studies have indicated that combining the actions of two drugs working on different neurobiological circuits may produce an additive reduction in alcohol craving and/or consumption. Therefore, it is not possible to rule out that the integration of neuropharmacology and psychoneuroendocrinology may lead to identifying combinations of medications working on different targets with a consequent higher reduction in alcohol craving and/or consumption. Our experiments provide data integrating pharmacological and neuroendocrinological findings in order to understand and treat alcohol craving and dependence. These studies could get the basis for more sophisticated neuropharmacological/neuroendocrinological approaches, including simultaneously treatment studies, laboratory studies, imaging tests and others.

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