European Neuropsychopharmacology (2017) 27, 42–47

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Association of plasma calcium concentrations with alcohol craving: New data on potential pathways

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Received 15 June 2016; received in revised form 9 November 2016; accepted 11 November 2016

KEYWORDS
Alcohol dependence;
Calcitonin;
Calcium;
Craving;
Parathyroid hormone;
Vitamin D

Abstract
Recently, calcium was suggested to be the active moiety of acamprosate. We examined plasma calcium concentrations in association with severity of alcohol dependence and its interaction with regulating pathways and alcohol craving in alcohol-dependent patients. 47 inpatient alcohol-dependent patients undergoing detoxification treatment underwent laboratory testing, including calcium, sodium, liver enzymes as well as serum concentrations of calcitonin, parathyroid hormone and vitamin D. The psychometric dimension of craving was analyzed with the Obsessive Compulsive Drinking Scale (OCDS). The severity of withdrawal was measured with the Alcohol Dependence Scale (ADS) and with the Alcohol Dependence Scale for high-risk sample (ADS-HR). The main findings of our investigation are: a) a negative correlation of plasma calcium concentrations with alcohol craving in different dimensions of the OCDS; b) a negative correlation of plasma calcium concentrations with breath alcohol concentration; c) lowered calcitonin concentration in the high-risk sample of alcoholics; d) lowered plasma vitamin D concentrations in all alcoholic subjects. Our study adds further support for lowered plasma calcium concentrations in patients with high alcohol intake and especially in patients with increased craving as a risk factor for relapse. Lowered calcitonin concentrations in the high-risk sample and lowered vitamin D concentrations may mediate these effects. Calcium supplementation could be a useful intervention for decreasing craving and relapse in alcohol-dependent subjects.

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http://dx.doi.org/10.1016/j.euroneuro.2016.11.007
0924-977X/

1. Introduction

Acamprosate is one of the available drugs for reducing craving in people suffering from alcohol addiction. Recent results have suggested calcium as the active moiety of acamprosate and therefore responsible for the anti-craving effect of acamprosate (Spanagel et al., 2014). Shown in animal models, alcohol-dependent rats receiving calcium or calcium-acetylhomotaurinate showed less alcohol-seeking (a model of craving) and relapse behavior than rats with sodium or sodium-acetylhomotaurinate administration. Furthermore in the clinical part of the aforementioned survey, patients with higher plasma calcium concentrations under acamprosate treatment showed longer time to relapse and cumulative abstinence compared to those receiving placebo treatment. The results by Spanagel et al. (2016) initiated a controversial debate (Kufahl et al., 2014; Mann et al., 2016). While Mann and colleagues found no correlation between plasma calcium concentrations and treatment outcome, Spanagel et al. (2016) argued that the sample by Mann et al. (2013) could not be used to prove their conclusions since it was underpowered and failed to show any treatment effect of acamprosate in comparison to placebo treatment.

Calcium is crucial to many functions of physical health. Roughly 99% of calcium in the body is located in bones and teeth; thus the skeleton is a calcium reservoir (Areco et al., 2015; Emkey and Emkey, 2012). Only 1% of total calcium is located in serum, and is tightly regulated by a complex metabolic process involving the intestine, kidney, bone and parathyroid glands, which primarily consists of the calciotropic factors: calcitonin, vitamin D and parathyroid hormone (PTH) (Fleet and Schoch, 2010).

Calcitonin is a peptide hormone, produced in the parafollicular cells (C-cells) of the thyroid gland (Hirsch et al., 1963). As an antagonist to PTH, calcitonin reduces the serum calcium concentrations (Carney, 1997). The hypocalcemic effect of calcitonin depends on inhibiting osteoclast activity. The implications of calcitonin for daily calcium balance are still in discussion. Calcitonin treatment has been shown to be limited by tachyphylaxis arising after several days of treatment, due to the downregulation of calcitonin receptors (Stone et al., 1992).

Acute alcohol ingestion leads to an increase in plasma calcitonin concentrations, while chronic alcohol consumption and detoxification show variable effects (Ilias et al., 2011; Rico, 1990; Vantyghem et al., 2007). Regulating calcium homeostasis involves the parathyroid gland detecting decreased calcium concentrations and stimulating synthesis of vitamin D in the kidneys, thus increasing renal calcium absorption and calcium bone reabsorption (for an overview s. Kopic and Geibel (2013)). The importance of vitamin D for intestinal calcium entry is verified by vitamin D-deficient patients, who ingest as much as 80% less calcium from their food compared to healthy persons (Sheikh et al., 1988). In addition to its role in the intestine, in a similar way vitamin D upregulates proteins that increase renal calcium reabsorption. In healthy individuals calcitriol lowered PTH levels but did not change calcium excretion (Hafner et al., 2008).

Vitamin D controls PTH through a negative-feedback loop at a transcriptional level (Russell et al., 1993). PTH is synthesized and stored in secretory vesicles in the parathyroid glands and released in response to low plasma calcium concentrations. Slight changes in the concentrations of calcium result in detrimental effects concerning the excitability of neurons and muscles. The fine regulation of calcium hemostasis is highlighted by the low plasma half-life of PTH (5 min) (Bieglmayer et al., 2002). Through permanent monitoring of plasma calcium concentrations, the calcium-sensing receptor triggers, among other effects, PTH release. Chronic calcium deficiency, as a result of defective intake or weak intestinal absorption, can lead to diminished bone mass and osteoporosis (Beto, 2015).

Chronic alcohol consumption is known for its association with vitamin D deficiency, with reduced intestinal calcium absorption and bone density in alcohol-dependent patients (Luisier et al., 1977; Zhu and Prince, 2015). Lower plasma calcium concentrations have been shown in alcohol-dependent patients with and without hepatic cirrhosis (Vodoz et al., 1977), leading to alterations in bone mineral density such as osteoporosis and osteopenia (Lopez-Larramona et al., 2013). Moreover, Laitinen et al. (1994) found a malfunction in the parathyroid glands in response to a hypocalcemic stimulus in alcohol-dependent patients during intoxication (Laitinen et al., 1994). Already in the year 1952, O'Brien showed that intravenous administration of calcium (called calmonose) reduces the physical withdrawal symptoms in alcohol-addicted patients (O'Brien, 1952, 1964). He suggested that calcium could be involved in behavior that leads to craving and alcohol consumption. Pathways remained unclear and no further studies have been conducted.

The aim of the present study was to investigate possible associations between plasma calcium concentrations and other hormone concentrations such as calcitonin, vitamin D and PTH and psychopathological burdens in patients with alcohol dependence. Therefore, we examined plasma concentrations of calcium at onset of detoxification treatment and psychometric dimensions for assessing symptoms related to alcohol dependence, such as craving and the severity of dependence.

2. Experimental procedures

2.1. Participants

47 inpatient alcohol-dependent patients undergoing detoxification treatment at the Department of Addictive Behavior and Addiction Medicine at the Central Institute of Mental Health in Mannheim, Germany were in included in the study.

All patients fulfilled the diagnostic criteria for alcohol dependence according to the ICD-10 (International Classification of Diseases, 10th revision) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition). Potential existing comorbidities and clinically relevant somatic and psychological symptoms were assessed with the BSI (Derogatis and Spencer, 1982), a short version of the SCL-90 (Symptom Checklist-90) containing nine subscales. All patients were free of psychiatric medication, including antipsychotics and antidepressants, for at least 3 months prior to the study. Withdrawal symptoms were treated with benzodiazepines (diazepam or lorazepam) if necessary. All patients were hospitalized and remained at the hospital during the study.