European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

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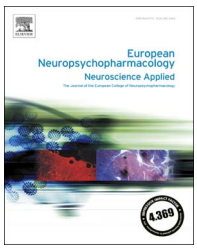

Association of plasma calcium concentrations with alcohol craving: New data on potential pathways

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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.

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The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the University Medical Centre in Mannheim, Germany. All patients gave written informed consent after the procedure had been fully explained to them and prior to their inclusion in the study.

2.2. Hormone measurements

Blood was drawn on day 1 of detoxification treatment at 8.00 a.m. before breakfast, after the patient had fasted overnight, and under standardized conditions. These blood samples were used for testing calcium, sodium, gamma glutamyl transferase (γGT), aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) concentrations as well as serum concentrations of calcitonin, PTH and vitamin D. Ethylenediaminetetraacetic acid (EDTA)-blood samples were centrifuged immediately after drawing blood. All blood samples were aliquoted and stored at −80 °C (Witt et al., 2016). All serum values were determined using the DuoSet enzyme-linked immunosorbent assay (ELISA). Serum concentrations of calcitonin, PTH and vitamin D were measured with a radioimmunoassay kit (Cobas, Roche, Mannheim, Germany). The detection limit of calcitonin was 0.5 pg/ml. The inter-assay coefficient of variation was <2.4%; the intra-assay coefficient was <2.3%. The detection limit of PTH was 1.20 pg/ml. The inter-assay coefficient of variation was <2.3%; the intra-assay coefficient was <2.1%. The detection limit of vitamin D was 3.00 ng/ml. The inter-assay coefficient of variation was <7.5%; the intra-assay coefficient was <7.3%.

2.3. Psychometric assessment

Psychometric data were sampled on day 1 of detoxification. The data were acquired directly after collecting blood samples and assessed using a structured interview. All patients answered to a test battery, including the following psychometric assessments:

Obsessive Compulsive Drinking Scale (OCDS): Measurement of craving in patients suffering from alcohol dependence (Anton et al., 1996). The 14 items of the OCDS examine alcohol-related thoughts, psychosocial disturbances, and impaired control of drinking. The five possible responses per item (0-4) reflect increasing symptom-intensity. Two subscales - "obsessions" and "compulsions" - are used to summarize items 1-6 and 7-14, respectively. The obsession subscale is believed to represent the cognitive preoccupation with alcohol for subjects suffering from an alcohol-use disorder, while the compulsion subscale is thought to account for the behavioral and motivational aspects of alcohol consumption (Mann and Ackermann, 2000).

Alcohol Dependence Scale (ADS): A self-rating questionnaire consisting of 25 items including alcohol-withdrawal symptoms, impaired control over drinking, awareness of compulsions to drink, increased alcohol tolerance and salience of drink-seeking behavior (Skinner and Horn, 1984).

Alcohol Dependence Scale high-risk sample (ADS-HR): A 9-item version of the 25-item ADS, which discriminates between those with no or minimal alcohol problems and those with symptoms of excessive or abusive drinking (Kahler et al., 2003). The severity of alcohol dependence is characterized by items dealing with the amount of last drinking episode, the heaviness of drinking after abstinence and failing to cut down drinking, for example.

2.4. Statistical analysis

Results of psychometric data, plasma calcium concentrations and hormone levels were presented as mean±SD (standard deviation). Associations between psychometric measurements and serum concentrations were investigated using Pearson's correlation coefficient. Stepwise linear regression analyses were applied to identify the influence of hormone concentrations on craving (OCDS). We set OCDS as dependent and the hormone concentrations (calcitonin, parathyroid hormone, calcium and vitamin D) as independent variables.

In a second analysis we performed a median split of the ADS-HR to identify the subgroup of severely dependent alcoholics. Hormone concentrations were compared with *t*-tests for independent samples.

p-Values of less than 0.05 (two-tailed) were considered indicative of statistical significance. Data was analysed using IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp.). Data are presented using Graph Pad Prism 6 (Graph Pad Inc., San Diego, CA).

3. Results

3.1. Sample characteristics

We included 47 alcohol-dependent patients with a mean duration of alcohol dependence of 13.35 (±12.28) years and a mean intake of 172.81 (±108.10) g of alcohol per day. Participants' characteristics are shown in Table 1.

3.2. Psychometric measures

ADS and ADS-HR were highly associated with the number of detoxification treatments (ADS: $r=0.36$, $p=0.01$; ADS-HR: $r=0.45$, $p<0.001$). ADS and ADS-HR showed significant correlation ($r=0.84$, $p<0.001$). Mean and standard deviation are shown in Table 1. Plasma calcium concentrations were negatively correlated with breath alcohol concentration at admission for detoxification treatment ($r=-0.27$, $p=0.04$).

Table 1 Participants' characteristics and laboratory parameters.

	Mean±SD
Age [years]	46.38 (9.92)
% women	19,10%
BMI [kg/m^2]	24.24 (4.00)
Smoking [cigarettes/day]	22.53 (15.57)
Duration of addiction [years]	13.35 (12.28)
Alcohol [g/day]	172.81 (108.10)
Number of detoxifications	2.41 (2.12)
Breath alcohol at admission [‰]	1.14 (1.02)
ADS	15.35 (6.61)
ADS-HR	7.17 (3.74)
OCDS sumscore	25.72 (9.55)
Calcium (2.15-2.55 mmol/l)	2.39 (0.13)
Calcitonin male (<9,5 µg/l)	4.48 (3.79)
Calcitonin female (<6,4 µg/l)	0.10 (0.0)
PTH (11-43 ng/l)	34.73 (15.86)
25-OH-Vitamin D3 (20-70 pg/ml)	11.47 (15.86)
GGT (0-40 U/l)	367.74 (629.12)
ASAT (0-35 U/l)	79.72 (66.63)
ALAT (0-35 U/l)	64.57 (47.82)

Data are presented as mean (SD) or frequency (%), *kg* kilograms, *m* meters, *g* gram, ‰ per mill, *mmol* millimole, *l* litre, *µg* microgram, *ng* nanogram, *pg* picogram, *ml* millilitre, *U* Unit.

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Table 2 Association between craving and calcium concentration measured with the OCDS.

	r	*p*
OCDS sumscore	−0.38	0.008
OCDS current craving	−0.36	0.01
OCDS obsession subscale	−0.31	0.03
OCDS compulsion subscale	−0.4	0.006

OCDS Obsessive Compulsive Drinking Scale, *r* Pearsons' correlation coefficient, *p* value of significance.

3.2.1. Association between calcium associated humoral markers and craving

We found negative correlations between calcium concentrations and craving (OCDS and its subscales), summarized in Table 2.

In a stepwise linear regression analyses calcium showed a significant effect on craving (OCDS sumscore) ($F=7.635$, $p=0.008$) with an explained variance of 15% (adjusted $R^2=0.126$). In this linear regression model, only plasma calcium levels showed a significant influence (beta coefficient for the plasma calcium concentrations was: −0.381), PTH, vitamin D and calcitonin showed no influence on craving (see Fig. 1).

3.3. Hormone measurements and correlations

Hormone measurements and liver enzymes are shown in Table 1. Mean calcium, PTH and calcitonin concentrations were in the normal range. Calcium and calcitonin correlated positively ($r=0.284$, $p=0.037$). PTH was negatively correlated with vitamin D ($r=-0.449$, $p<0.001$). All participants showed reduced plasma vitamin D concentrations.

3.4. Combined hormone and psychometric analyses

After a median split of the ADS-HR scale (median=7), we compared plasma concentrations of calcium, calcitonin PTH and vitamin D between the two subgroups. Calcitonin concentrations differed significantly ($t=2.267$, $p=0.02$) (subgroup with lower values of the ADS-HR: mean: 2.34 μg/l, SD: 2.19 μg/l; subgroup with upper values of the ADS-HR: mean: 4.82 μg/l, SD: 4.53 μg/l; Fig. 2).

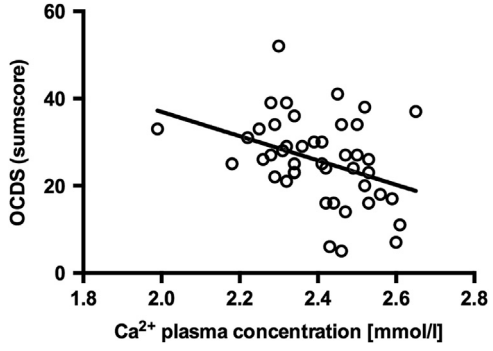

Fig. 1 Association between calcium concentrations and severity of alcohol dependence. Figure shows a negative association between calcium plasma concentrations and craving, regarding the OCDS sumscore.

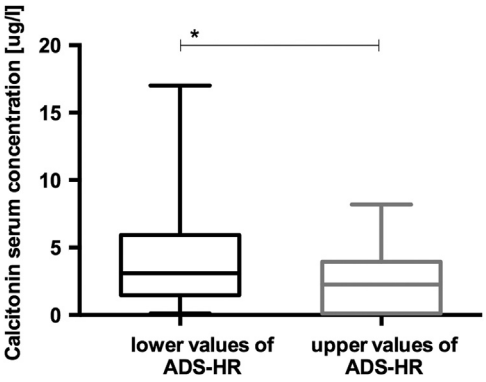

Fig. 2 Hormone specialties in the high-risk sample of alcoholics. Comparing the two subgroups of the ADS high-risk sample after median split, we found a significant difference (*$p=0.02$), (subgroup with lower values of the ADS-HR: mean: 2.34 μg/l, SD: 2.19 μg/l; subgroup with upper values of the ADS-HR: mean: 4.82 μg/l, SD: 4.53 μg/l).

4. Discussion

We focused on the research question of whether plasma calcium concentrations in alcohol-dependent subjects are associated with alcohol craving and whether the regulation of calcium metabolism mediates this effect. Based on the main results of our study that: a) a negative correlation of plasma calcium concentrations with alcohol craving; and b) a negative correlation of plasma calcium concentrations with breath alcohol concentration at admission, we suggest that the severity of intoxication with alcohol and the severity of alcohol dependence might induce lower calcium concentrations that are associated with craving in alcohol-addicted patients.

Further results are: c) decreased calcitonin concentrations in the "heavily drinking" subgroup; and d) significantly reduced plasma vitamin D concentrations in all alcoholic subjects.

We found a significant difference between calcitonin serum concentrations when comparing the subgroups of the nine-item Alcohol Dependence Scale for a high-risk sample (Kahler et al., 2003). The scale highlights symptoms of delirium and the severity of alcohol dependence characterized by items dealing with the amount and heaviness of drinking and even failing to cut down. Acute alcohol ingestion results in an increase in plasma calcitonin concentrations while chronic alcohol consumption and detoxification showed variable effects (Ilias et al., 2011; Rico, 1990; Vantyghem et al., 2007). Our findings on calcitonin indicate a significant difference among alcohol-dependent patients with respect to the severity of dependence. While our study examined alcoholics during early detoxification treatment from alcohol, we surmise an influence of calcitonin mainly in severely affected alcoholics, inducing a decrease of calcium concentrations. The regulatory role of calcitonin for the adaptation of calcium concentrations is discussed controversially. In animal models it was shown that after thyroidectomy, serum calcitonin concentration

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was not affected (Cooper et al., 1970). The physiological role of calcitonin is still questionable, with speculations that its role is rather evolutionary and the current physical is not as well as important for human (Hirsch and Baruch, 2003). There is evidence for the importance of calcitonin during times of high calcium necessity, for example during lactation (Woodrow et al., 2006). During pregnancy and lactation, calcitonin seems to be osteoprotective by inducing the renal synthesis of vitamin D (Zhong et al., 2009). Calcitonin was also thought to act on the collecting duct in a way similar to that of antidiuretic hormone (ADH), concentrating the urine by upregulating reabsorption (de Rouffignac and Elalouf, 1983).

Recently, a translational study evaluating the pharmacodynamics of acamprosate put the focus on the role of calcium in the treatment of alcohol addiction (Spanagel et al., 2014). Calcium substitution was associated with lowered relapse rates and higher cumulative abstinence rates in alcohol-dependent patients. Earlier studies establishing an association between heavy alcohol consumption and lowered bone density pointed out the critical role of calcium metabolism in heavy alcohol intake (Gonzalez-Reimers et al., 2015; Lopez-Larramona et al., 2013). Gonzalez-Reimers and colleagues recommend vitamin D and calcium supplementations in alcohol-dependent patients with bone changes and liver disease, in addition to alcohol abstinence and nutritional assessments in order to improve bone metabolism. Excessive alcohol consumption is an important risk factor for bone density and fracture possibility due to interactions with estrogens, calcium and vitamin D (Fini et al., 2012). On the other hand, high vitamin D concentrations and low calcium intake could increase bone reabsorption, and bone mineralization would decrease in order to maintain balanced calcium concentrations. Further investigations are necessary for examining the clinical outcome of vitamin D and calcium supplementation in alcohol-dependent patients, as the implications of such supplements are still being debated and the current research findings are not definite (Carmeliet et al., 2015). To achieve normal concentrations of calcium from hypocalcaemia, PTH and vitamin D are necessary, with their associated target organs (intestine, kidney and bone). The results concerning serum concentrations of PTH and vitamin D are in line with current data, which show that vitamin D concentrations are negatively associated with PTH and alcohol consumption (Olmos et al., 2016).

There is evidence for an interaction between calcium's role in genetic regulation and gene expression, and alcohol consumption. For example, McClintick et al. (2016) found in male adolescent alcohol-preferring rats five calcium ion channels to be variably expressed. Moreover, a genome-wide association study demonstrates that the calcium signaling pathway in alcohol dependence is essential for the regulation of brain function, and that genes in this pathway are linked to having a depressive effect on alcohol consumption (Li et al., 2014). Calpain, belonging to the family of calcium-binding proteins, showed influence in alcohol-seeking and relapsing rats (Vengeliene et al., 2015). The authors suggest regulating the effects of calpains as a new potential pharmacological intervention in order to reduce craving and relapse in alcohol-dependent patients. Further studies are needed in order to strengthen the understanding of the complex interactions between hormone regulation and addictive behavior, especially the link between peripheral hormone concentrations and brain function.

5. Conclusion

Based on the current data and our results we stress the necessity of sampling prospective clinical data on short-term as well as long-term effects of calcium, in addition to vitamin D administration, in alcohol-dependent patients. Calcium supplementation might be a favorable target for decreasing craving and relapse behavior in alcohol-dependent patients.

Role of the funding source

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Contributors

Author AK, MG, FK designed the study and wrote the protocol. Author RiS, AK managed the literature searches and analyses. Authors RiS, AK, IR, RaS and FK undertook the statistical analysis, and author RiS and FK wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

We gratefully acknowledge Joy Fest for language editing. We also express our thanks to all participants in this study.

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Please cite this article as: Schuster, R., et al., Association of plasma calcium concentrations with alcohol craving: New data on potential pathways. European Neuropsychopharmacology (2016), http://dx.doi.org/10.1016/j.euroneuro.2016.11.007