Oxidoreductive homeostasis in alcohol-dependent male patients and the risk of alcohol drinking relapse in a 6-month follow-up

Jacek Budzyński [a,b,*], Marcin Ziółkowski [c], Maria Kłopocka [a], Damian Czarnecki [c]

[a] Chair of Vascular and Internal Diseases, Faculty of Health Sciences, The Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland
[b] Clinic of Vascular and Internal Diseases, Jan Biziel University Hospital No. 2 in Bydgoszcz, Poland
[c] Department of Psychiatric Nursing, Faculty of Health Sciences, The Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Poland

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ABSTRACT

Disturbances in the central signaling of reactive oxygen species (ROS) in response to energy intake are recognized as taking part in appetitive and consummative phases of eating disorders. This study aimed to verify the hypothesis that blood oxidoreductive balance can also affect demand for energy substances, such as alcoholic beverages in alcohol-dependent individuals, as well as the severity of their alcohol dependence and risk of drinking relapse. The following values were determined in the blood of 54 alcohol-dependent male patients after alcohol withdrawal, again after 4 weeks and after 6 months: the aldehyde products of lipid peroxidation (malonyl dialdehyde [MDA] and 4-hydroxynonenal [4-HNE]), nitric oxide (NO) metabolites, total antioxidant status (TAS), the blood activities of glutathione peroxidase (GSHpx), superoxide dismutase (SOD), glutathione reductase (GSHred), blood glucose, and lipids. Alcoholics who relapsed during 6 months of observation (n = 31, 57%) compared with patients who maintained alcohol abstinence for 6 months (n = 23, 43%) differed only in relation to initial and final NO metabolite serum concentrations. The risk of alcohol drinking relapse was lower in patients with an above-median initial blood concentration of NO metabolites and TAS. The oxidative stress parameters correlated with alcohol-dependence severity markers. No significant correlations between the studied antioxidant balance parameters and markers of nutritional status, including blood glucose and lipids, were found. Although the results of our study have some limitations and require further investigation, they suggest the role of oxidoreductive balance in the pathomechanisms of alcohol dependence and drinking relapse. In addition, due to a lack of association found between blood oxidative stress parameters and BMI, blood glucose, and lipid concentrations, they show the presence of disturbances in systemic ROS signaling in response to energy availability in alcoholics after alcohol withdrawal.

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Introduction

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the products of metabolic processes in many organs and tissues (Comporti et al., 2010; Drougard, Fournel, Valet, & Knauf, 2015). They can act both as favorable substances that, for example, help to kill microorganisms, and as harmful substances that are involved in the pathogenesis of a number of diseases, such as diabetes mellitus, atherosclerosis, neurodegenerative disorders, chronic obstructive lung disease, and cancer (Bocci & Valacchi, 2013; Haas, Ye, & Löhr, 2012; Sotgia, Martinez-Outschoorn, & Lisanti, 2011; Varela-Rey, Woodhoo, Martinez-Chantar, Mato, & Lu, 2013). Oxidative stress is also recognized as participating in the pathogenesis of a number of psychiatric disorders, such as schizophrenia (Jorgensen et al., 2013), dystonia (Bijjal et al., 2012), anxiety (Hovatta, Juhila, & Donner, 2010), and depression (Vargas et al., 2013), as well as addiction to alcohol (Kopczyńska, Torliński, & Ziółkowski, 2001), nicotine (Vargas et al., 2013), methamphetamine (Huang et al., 2013), and heroin (Kovatsi et al., 2010).

Recent data show that ROS are not only responsible for the production of harmful modifications in DNA, cells, and tissue, but may also play a functional role and act as signaling molecules that regulate the release of neurotransmitters and synaptic plasticity in the brain, especially in the hypothalamus. Through this pathway, ROS are recognized as participating in the regulation of food intake,

* Corresponding author. Clinic of Vascular and Internal Diseases, Jan Biziel University Hospital No. 2 in Bydgoszcz, 75 Ujejskiego Street, 85-168 Bydgoszcz, Poland. Tel./fax: +48 52 36 55 148.
E-mail address: budz@cps.pl (J. Budzyński).

energy, glucose, and lipid metabolism (Drougard et al., 2015). After eating glucose or lipids or the infusion of these substances into the carotid artery, an increase in hypothalamic mitochondrial production of ROS was observed that generated an anorexic effect in rats (Leloup et al., 2006). This nutrient effect was neutralized by the simultaneous intra-arterial infusion of antioxidants, such as glutathione or vitamin E, which were recognized as confirming the importance of ROS in the pathomechanism of food intake regulation. The release of ROS in the hypothalamus is influenced by pancreatic and gut hormones (e.g., insulin, glucagon, and ghrelin), adipokines (e.g., leptin and apelin), neurotransmitters (e.g., dopamine and orexin), and nutrients (e.g., glucose and lipids) (Drougard et al., 2015), which suggests the importance of systemic and peripheral factors in the modulation of ROS signaling in the central nervous system, particularly as ROS also act in many of the signaling pathways in different peripheral organs.

Disturbances in ROS signaling pathways, expressed, for example, as a lack of increase in ROS production after food intake, is considered as one of the pathomechanisms of obesity and diabetes mellitus type 2. This process may also lead to imbalance in the autonomic nervous and neuroendocrine systems, which provokes overactivation of glycogenolysis and gluconeogenesis in the liver, resulting in fasting hyperglycemia (Drougard et al., 2015).

As ROS take part in the central and peripheral regulation of food intake, we assumed that oxidoreductive homeostasis in the blood could take part in mechanisms of alcohol craving (the appetitive phase of energy intake), alcohol dependence, and alcohol drinking relapse (the consummative phase of energy intake) after withdrawal therapy, not only locally in the hypothalamus, but also systemically. This hypothesis was based on the following data: (a) drinking alcohol is linked with the overproduction of ROS and a decrease in antioxidative defense level (Cahill, Wang, & Hoek, 1997; Chen, Pan, Chen, & Huang, 2011; Comporti et al., 2010; Grasseli et al., 2014; Guo, Yang, & Wu, 2008; Götz et al., 2001; Huang, Chen, Pan, & Chen, 2014; Huang, Chen, Peng, Tang, & Chen, 2009; Kopczyńska et al., 2001; Petitpas et al., 2013); (b) sustained ROS overproduction secondary to chronic alcohol abuse may lead to a decrease in the hypothalamus of the responsiveness of anorectic proopiomelanocortin (POMC) neurons to ROS signaling, which causes an impairment in energy intake inhibition via a negative feedback pathomechanism and promotes an increase in orexigenic neuropeptide Y (NPY) tone (Diano et al., 2011; Drougard et al., 2015); (c) an increase in orexigenic peptide activity occurs in the hypothalamus that stimulates feeding, i.e., increasing both fat and alcohol intake, via a positive feedback pathomechanism (Barson et al., 2009; Barson & Leibowitz, 2016; Bayerlein et al., 2011; Leibowitz, 2007; Rotter et al., 2012); and (d) alcohol overuse may stimulate a vicious cycle of both fat and alcohol intake and ROS overproduction. To test the role of ROS in the pathogenesis of alcohol abstinence and relapse, we analyzed parameters of oxidoreductive homeostasis in the blood of alcohol-dependent male patients during a 6-month observation period in relation to indices of body energy homeostasis (anthropometric nutrition status markers, blood lipids, and glucose concentrations), as well as parameters of alcohol-dependence severity.

Materials and methods

Fifty-four alcohol-dependent male patients were involved in the study. The inclusion criteria were as follows: male sex, aged 30–50 years, satisfaction of ICD-10 criteria for alcohol dependence, the motivation to maintain abstinence and having finished a period of alcohol abuse no less than 14 days before the beginning of the study. The exclusion criteria were as follows: concomitant presence of diseases that could have an influence on oxidative balance (e.g.,

acute or chronic inflammatory processes or neoplasm), psychotic or dementia disorders, addiction to substances other than alcohol (except nicotine), and the use of any medicines.

Blood samples for biochemical determination were taken from all the patients after 14 h of fasting at the start of the study, and again after 4 weeks and then 6 months of abstinence. The blood concentration of aldehyde products of lipid peroxidation (MDA and 4-HNE) was determined by a calorimetric method using the Bioxytech LPO-586™ assay from Oxis International. Total antioxidant status (TAS), and blood levels of glutathione peroxidase (GSHpx), superoxide dismutase (SOD), and glutathione reductase (GSHred) were determined using a calorimetric method in accordance with the manufacturer's instructions (laboratory sets from Randox). The blood concentration of nitric oxide (NO) metabolites (nitrites and nitrates) was determined using a colorimetric method using an EPPOL 20 photometer and laboratory set from Boehringer Mannheim (Nitric Oxide Colorimetric Assay). The reference values for the antioxidant status parameters determined by the assay producers are presented in Table 1.

The following glucose and lipid concentrations, as energy substrates, were also determined from the blood samples: total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides (TGL). Also estimated was peripheral blood morphology, as well as biochemical markers of alcohol abuse levels, such as the activity of γ-glutamyltranspeptidase (GTP), aspartate aminotransferase (AST), alanine transferase (ALT), and mean corpuscular volume (MCV).

For the first 8 weeks of the study, all the alcohol-dependent patients were hospitalized in the same Addiction Therapy Unit. They received a similar hypolipidemic diet that was in accordance with European Atherosclerosis Society (1992) recommendations (Pyörälä, De Backer, Graham, Poole-Wilson, & Wood, 1994). Energy consumption was, on average, 2000 kcal per day, but in patients with a body mass index (BMI) above 25 kg/m^2, a reduced diet (20 kcal/kg body mass) was recommended. Their daily diet consisted of 33% cereal products, 25% vegetables, 15% milk products, and the rest in meat, fish, or legumes. In this way, daily cholesterol consumption was lower than 300 mg and daily fat-energy consumption was approximately 30% (saturated fatty acids below 10%, monounsaturated fatty acids were 10–15%, and polyunsaturated fatty acids were 7–10% of energy intake). In patients with a BMI above 25 kg/m^2 and in those with hypertriglyceridemia (TGL > 150 mg/dL), no simple sugar consumption was recommended. The patients did not use medication for the duration of the study period.

The following psychometric scales were used in the study: the Short Alcohol Dependence Data (SADD) Questionnaire (Raistrick, Dunbar, & Davidson, 1983), the Michigan Alcoholism Screening Test (MAST) (Teitelbaum & Mullen, 2000), the Toronto Alexithymia Scale (Bagby, Parker, & Taylor, 1994), and the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

Maintenance of alcohol abstinence was controlled during hospitalization on the basis of physical examination, as well as the presence of alcohol in exhaled air and the determination of the above-mentioned biochemical markers of alcohol-abuse level. Following discharge from the ward, 8 weeks after the start of the study, abstinence maintenance was diagnosed on the basis of interviews, the level of biochemical markers of alcohol abuse, objective familial interviews, and medical documentation analysis (from the outpatient department).

Measured outcomes

- Maintenance of alcohol abstinence 4 weeks and 6 months after inclusion in the study.