E5

Effects of ibogaine treatment on redox homeostasis and energy metabolism in rat

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Ibogaine is the main alkaloid in the root barks of *Tabernanthe iboga* plant which groves in Western-Central Africa. It has been used by natives to overcome fatigue, hunger and thirst, and in higher doses to provoke hallucinations. In the "ibogaine medical subculture" in Europe and America it is used to facilitate abstinence from variety of addictive substances (cocaine, heroin, methadone, alcohol. . .). It was hypothesized that adaptive changes in ATP-related cell energy homeostasis are important contributing factor, to ibogaine's anti-addictive activity. Examinations on different experimental models showed that ibogaine caused rapid depletion of ATP accompanied by increased production of reactive oxygen species and the activation of antioxidative enzymes, as well as upregulation of energy related enzymes. Our goal was to investigate the effects of ibogaine oral application on redox balance in rat brain and energy metabolism in liver. The later was estimated by accessing amount of glycogen reserves. The null hypothesis was that ibogaine had no effect on the activity of antioxidative enzymes, concentration of lipid peroxides and free sulfhydryl groups in rat brain, or on the amount of glycogen in liver. In this study 3–month-old female Wistar rats were treated with a single dose 20 mg/kg body weight of ibogaine *via* gavage. Rats were sacrificed 6 or 24 h after treatment; brain and perfunded liver samples were homogenised and sonicated. Liver sample was also prepared for histological analysis. We measured the activities of antioxidative enzymes, namely total superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GR) and the activity of glutathione S-transferases (GSTs) a xenobiotic detoxification enzyme family member. Concentrations of thioarbituric acid reactive substances (TBARS) and protein and nonprotein free sulfhydryl groups (–SH) were measured in brain sonicates. Amount of glycogen in liver was determined based on PAS staining. Results were analysed by One-way ANOVA with Tukey's HSD post hoc test, $p < 0.05$. There were no significant changes of measured antioxidative enzymes activity in brain neither 6 nor 24 h after treatment with ibogaine. Also, total activity of GSTs remained unaltered. On the other hand, concentration of TBARS was significantly increased 6 h after treatment while after 24 h TBARS concentration was the same as in controls. Treatment with ibogaine caused an increase of protein free –SH groups concentration which was more pronounced after 24 h. However, the concentration of nonprotein free –SH groups was decreased in brain of treated rats but also more prominently after 24 h. Histological analysis of liver showed that amount of glycogen was decreased in treated rats. Glycogen depletion in the liver of treated rats was greater in 6 h group compared to 24 h group. Increased concentrations of TBARS suggest increased lipid in brain of treated rats. Decreased concentration of nonprotein free –SH groups suggests decreased concentration of reduced glutathione, the main source of nonprotein –SH groups in cells. These findings coincide with ibogaine-induced transient burst in cellular respiration followed by intensive production of reactive oxygen species, described in literature. Despite these indicators of oxidative stress there is no change in the activity of any antioxidative enzyme, not even after 6 h. Unaltered activity of GSTs suggest that applied dose of ibogaine doesn't have an acute toxic effect on brain. Finally, alterations in glycogen amount in hepatocytes suggest a transient depletion of energy reserves, which are on their way to recovery already 24 h after treatment. All of the aforementioned suggest that after oral administration of ibogaine there is rapid transient changes in redox and energetic homeostasis in brain similar to those described on other experimental models. It seems that antioxidative defense system is capable to preserve redox homeostasis within first 6 h, but some consequences in the form of oxidative damageare still present. Since these are all energy-intensive processes, required energy may have been obtained at the expense of liver glycogen. Having in mind a proposed role of energetic and redox related changes in anti-addictive effects of ibogaine, it is essential to investigate redox balance and energy metabolism in brain within the first hours after ibogaine application.

Keywords: Anti-addictive; Oral administration; Brain; Liver; Antioxidative enzymes.

Ethical approval: The procedures applied in this study complied with directive 2010/63/EU on protection of animals used for experimental and other scientific purposes, and approved by the Ethical Committee for the Use of Laboratory Animals of the Institute for Biological Research "Siniša Stanković" University of Belgrade, decision No. 02-03/16.

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E6

Investigation of neuropharmacological and in-vitro antioxidant activities of hydroethanolic bulb extract of *crinum glaucum* a. chev. (amaryllidaceae) in mice

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Crinum glaucum A. Chev (Amaryllidaceae)is a bulbous plantused locally in the management of convulsion and mental disorder. This study was carried out to investigate the neuropharmacological and in-vitro antioxidant activities of the hydroethanolic bulb extract of *Crinum glaucum* (CG). Two sets of mice comprising 7 groups ($n = 6$) each were subjected to oral treatment with fluoxetine (64 mg/kg) and CG (50, 100, 200 and 400 mg/kg) for 21 days. The first set of mice were subjected to open field test (OFT) and forced swim (antidepressant) test (FST). The second set of mice were subjected to hole-board test (HBT) and tail suspension (antidepressant) test (TST). All tests were carried out on day 0, 1, 7, 14 and 21. After day 21, the mice were sacrificed and the brains assessed for monoamines and histopathology. In-vitro antioxidant analysis of CG was done using 2,2–diphenyl–1–picrylhydrazyl (DPPH) radical scavenging, metal chelating and ferric reducing antioxidant power (FRAP) assays. Acute toxicity and phytochemical screening of CG were also carried out. At 50 mg/kg, CG significantly ($p < 0.05$) increased the number of sectional crossings on day 1 and 21, and number of assisted rearings on day 14 in OFT relative to control. At this dose, the extract significantly reduced ($p < 0.05$) the duration of immobility on day 1 in FST compared to control, as also observed at the dose of 400 mg/kg. CGat 100 mg/kg on day 21