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Metabolic plasticity and the energy economizing effect of ibogaine, the principal alkaloid of *Tabernanthe iboga*

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ABSTRACT

Ethnopharmacological relevance: The root bark of iboga plant—*Tabernanthe iboga* has been used traditionally in Central Africa as a psychoactive substance in religious rituals, while in smaller doses it is appreciated due to its stimulant properties. The iboga root bark, iboga extract or pure ibogaine are being recognized in the West as an anti-addiction remedy and their use is increasing.

Aim of the study: Our previous studies have demonstrated a transient ATP pool reduction under ibogaine accompanied by the induction of energy metabolism related enzymes. The present study aimed to find the cause of this energy deprivation and to foresee its immediate and long-term impact on metabolism.

The overall project is designed to disclose the common mechanism of action at these seemingly diverse indications for iboga use, to predict eventual adverse effects and to build the grounds for its safe and beneficial utilization.

Materials and methods: The rate of carbon dioxide (CO_2) as a marker of energy metabolism in stationary yeast model under aerobic conditions in the presence of ibogaine at concentration of 1, 4 and 20 mg/l was measured for 5 h by gas chromatography. The overall oxidative load was determined fluorimetrically by 2′,7′-dichlorofluorescein diacetate (H_2DCFDA) and *in vitro* antioxidant properties of ibogaine were defined by 1,1-diphenyl-2-picrylhydrazyl (DPPH) test.

Results: The CO_2 production under ibogaine was temporarily increased in a dose dependent manner.

The increased energy consumption as an early effect of ibogaine was proven by the fact that in spite of energy mobilization, the ATP pool has been simultaneously decreased.

Although increased cellular respiration co-produces reactive oxygen species (ROS), the overall oxidative load was significantly lowered by ibogaine. Since ibogaine does not show any significant *in vitro* antioxidant properties, the results indicate its stimulating influence on physiological oxidative stress defence system.

Conclusion: Ibogaine triggers remodeling of the housekeeping metabolism. Under the initial energy cost it results in increased efficacy of physiological antioxidative systems, which reduce oxidative damage and lowers basal metabolic needs. Together with induced catabolic enzymes they set a new metabolic equilibrium that saves energy and makes it easily available in case of extra needs. While healthy organism profits from improved fitness and mental performance and can withstand higher stress without risking a disease, due to the same principle ibogaine provides beneficial support at the recovery after diseases including addiction syndrome.

1. Introduction

Ibogaine is an indole alkaloid naturally found in the root bark of tropical rainforest shrubby plant iboga—*Tabernanthe iboga* Baill. (Apocynaceae family) and to a lesser extend in some other species of Tabernaemontana tribe. Iboga (tabernanthe radicis

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cortex) has been traditionally used in tribes of the Congo basin in Central Africa as a psychoactive sacrament used in the ceremony of initiation into adulthood. It induces trance and is considered to reveal one's purpose of life and his role in a society (Fernandez, 1982). In smaller doses it is appreciated due to its stimulant and aphrodisiac properties (Naranjo, 1969; Schultes, 1970). Hunters use it to promote vigilance while stalking pray (Fernandez, 1982). Its use is highly valued on long, tiring marches, on lengthy canoe voyages, and on difficult night watches (Schultes et al., 2001).

In the former century iboga extract under trademark Lambarene was sold in France and recommended as a tonic against fatigue, asthenia and depression and for recovery after infectious diseases (Goutarel et al., 1993). Other compositions containing ibogaine had been on the marked named Bogadin, Iperton, Endabuse (Ratsch, 1998).

In the last four decades the urban traditional use of iboga root bark, iboga extract or pure ibogaine is on the increase as an anti-addiction therapy (Alper et al., 2008). In the so called Ibogaine medical subculture it is used to ease the detoxification of drugs, for abstinence syndrome alleviation and to speed up the tolerance reversion. In long-term abstinence, it reduces craving for drugs by anxiety reduction and improvement of mood (Mash et al., 2000) and one of the explanations for this is psychoanalytical catharsis with resolution of inner conflicts (Naranjo, 1973). Existential insights resulting in social (re)integration of an individual are recognized as important consequence of iboga initiation in both native and Western societies (Fernandez and Fernandez, 2001). Besides, descriptions as spiritual revelation and religious redemption are not uncommon (www.ibogaine.co.uk/experience.htm) and interest for bare psycho-spiritual and religious use of iboga is so taking roots also in the West (www.sacrament.kibla.si). On the other hand *in vitro* and *in vivo* studies in animal models expose diverse biochemical impacts of ibogaine application (Alper, 2001; Maciulaitis et al., 2008).

Our recent work (Paškulin et al., 2010) showed that the induction of energy related enzymes in the yeast *Saccharomyces cerevisiae* accompanies the dose dependant decrease in ATP energy pool caused by ibogaine at concentrations of 1, 4 and 20 mg/l during 5 h. Yeast in stationary growth phase under aerobic conditions is an accepted model for studies of basic metabolic pathways of higher eukaryotes, including mammalian cells (Ma, 2001).

The aim of present study was to identify the cause and to foresee the consequences of ATP energy pool deprivation observed under ibogaine exposure, especially to confirm whether this energy shortage is a consequence of increased ATP consumption or it might be due to its silenced production. The rate of carbon dioxide (CO_2) production in yeast *Saccharomyces cerevisiae* in aerobic stationary growth phase was measured to define the level of oxidative catabolism and ATP production, under the concentrations of ibogaine that mirror those in the blood at different use—up to 1 mg/l corresponds to moderate stimulant effect, raising the dose brings psychoactive range and approaching 4 mg/l relates to the anti-addictive properties, while above are the traditional initiation doses (Fernandez and Fernandez, 2001; Mash et al., 2000). Parallel work on potential energy consumers like toxicity, oxidative stress and kinetics of ibogaine were conducted.

Our hypothesis was that ibogaine triggers energy consuming process and that there is a common denominator at diverse outcomes of iboga use.

2. Material and methods

2.1. Material

Ibogaine HCL was donated by Sacrament of Transition, Maribor, Slovenia. Ibogaine was used in our series of experiments since it is directly related to the iboga plant as its principal alkaloid. Besides, majority of literature concerns this pure form. The effect and after-effect of iboga root bark, its extract or pure ibogaine is except for kinetics reported as subjectively indiscriminative.

2.2. Yeast cultivation

Yeast *Saccharomyces cerevisiae* was cultivated in YEPD growth medium with the following composition: 10 g/l glucose (Kemika), 5 g/l yeast extract (Biolife), 5 g/l peptone (Oxoid), at 28 °C and 220 rpm to the stationary growth phase. Then cells were centrifuged for 5 min at 4000 rpm, washed with and resuspended in 50 mM potassium phosphate buffer, pH 7.0 to density of 1×10^8 cells/ml. The yeast culture was incubated at 28 °C and 220 rpm.

2.3. Cell CO_2 production

To determine cell respiration, 5 ml of 1×10^8 cells/ml yeast culture in 50 mM potassium phosphate buffer were transferred in sterile 15-ml serum bottles covered with airtight rubber stoppers. The suspension was incubated with ibogaine in concentrations of 0, 1, 4 and 20 mg/l at 150 rpm at 28 °C in the dark. The amount of CO_2 produced was measured at 0, 0.25, 0.5, 1, 2, 3, 4, and 5 h of incubation with gas chromatograph Hewlett Packard HP5890, as described by Odić et al. (2007). The chromatograph settings were as follows: column Porapak R mesh 100/120 (180 cm/1.8 in), oven temperature 50 °C, injector temperature 100 °C, TCD detector temperature 100 °C, carrier gas helium (180 ml min^{-1}), integrator HP3392A. The chromatograph was calibrated with an external standard having known CO_2 concentration. For each time point the results are expressed as relative difference in production of CO_2 by yeast cells under ibogaine compared to the control.

2.4. Estimation of oxidative stress

Intracellular oxidation was defined by using 2′,7′-dichlorofluorescein (H_2DCF), which is able to react with oxidants—reactive oxygen species (ROS) (Jakubowski and Bartosz, 1997).

Stationary phase yeast cells at concentration of 1×10^8 cells/ml were added H_2DCFDA as a stock of 1 mM ethanol solution to the final concentration of 10 μM. After incubation for 20 min at 28 °C, 220 rpm cells were treated with ibogaine in concentrations of 0, 1, 4 and 20 mg/l or ascorbic acid in *in-vitro* equipotent concentrations of 0, 1, 2 and 4 μM and samples were taken at the end of accelerated energy metabolism period. 200 μl of the cell suspension was transferred to the microplate and fluorescence was measured using Tecan microplate reader Safire II (excitation and emission wavelengths of 488 and 520 nm, respectively). The results are expressed as a relative difference in overall ROS load compared to the control:

$$\text{Ratio}\,[\%] = \left[E_{\text{treated}}/E_{\text{control}}\right] \times 100$$

where E is emission of ibogaine treated or control solution.

2.5. DPPH radical scavenging activity

The 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical is a stable radical with a maximum absorption at 517 nm that can readily undergo reduction by an antioxidant. Because of the ease and convenience of this reaction it now has widespread use in the free radical-scavenging activity assessment (Yamaguchi et al., 1998).

The reaction mixture (1 ml) contained 500 μl of daily prepared (1,1-diphenyl-2-picrylhydrazyl) DPPH solution (250 μM), 400 μl of Tris–HCl buffer pH 7.4 (100 mM) and 100 μl of various concentrations (10, 20, 40 and 80 μM) of ibogaine dissolved in distilled water. After thorough mixing, the solutions were kept in

the dark for 20 min at room temperature. Thereafter, the absorbance was measured at 517 nm. All tests were performed in triplicate, with trolox and ascorbic acid as physiological controls. The percent inhibition of the DPPH radical by ibogaine was calculated according to the formula:

$$\%\text{Inhibition} = \left[(A_{\text{blank}} - A_{\text{test}})/A_{\text{blank}}\right] \times 100$$

where A_{blank} is the absorbance of the DPPH in solution without test sample (antioxidant), and A_{test} is the absorbance of DPPH in solution with ibogaine.

2.6. Yeast viability

Cell viability was measured as cell-membrane integrity using LIVE/DEAD Funga Light™ Yeast Viability Kits (Molecular Probes), according to the manufacturer instructions. Briefly, the cells from 1 ml cell cultures were centrifuged (14,000 × *g*, 5 min) and washed once with filtered PBS, and cell suspensions at 1×10^6 cells/ml were prepared in PBS. Then 1 μl SYTO® 9 and 1 μl propidium iodide were added in the dark and the samples incubated at 37 °C for 30 min. After the incubations, the fluorescence was measured using a microplate reader (Tecan). The excitation/emission wavelengths for these two dyes are 480/500 nm for SYTO® 9 and 490/635 nm for propidium iodide.

2.7. Ibogaine kinetics

Yeast cells at a concentration of 1×10^8 cells/ml were suspended in different ibogaine buffer solutions (0, 1, 4, 20 mg/l) and incubated at 28 °C. Samples were taken in 15 min intervals, prepared and adequately diluted for analysis according to a modified method which was initially developed for the determination of ibogaine and noribogaine (internal standard prazepam) in biological samples (Koželj, 2010). The compounds were separated on Zorbax XDB-CN (75 mm × 4.6 mm i.d, 3.5 μm) by using an Agilent 1100 HPLC system and detected in the tandem quadrupole mass spectrometer Quattro micro™ API from Waters, the software used was MassLynx 4.1. All samples and standards were treated adequately to prevent decomposition of ibogaine and noribogaine due to daylight exposure.

3. Results

We have proceeded with our previous *in vivo* experiments on Wistar rats and yeast *Saccharomyces cerevisiae* in stationary growth phase in relation to ibogaine's influence on energy metabolism. In the present experiment, yeast in the same metabolic state was treated with 0, 1, 4 and 20 mg/l of ibogaine and CO_2 production was measured at 0.25, 0.5, 1, 2, 3, 4 and 5 h time points. Immediately after addition of ibogaine there was a dose dependent raise in CO_2 production with peak values of 16, 67, 142% (1, 4 and 20 mg/l of ibogaine, respectively) relative to control, which ceased in an hour and raised again between 2 and 4 h with second peak of 15, 11, 27% (1, 4 and 20 mg/l of ibogaine, respectively) at 3 h time point. After 3 h there was a progressive decline of CO_2 production crossing the control values at 4 h and dropping further until the end of experiment at 5 h, when reduction of the energy metabolism of 10, 9 and 31% (1, 4 and 20 mg/l of ibogaine, respectively) relative to the control was observed and further diminution expected through extrapolation from late trends (Fig. 1).

The total oxidative load in the enhanced catabolism part of the experiment was decreased by 24, 23, 57% (1, 4 and 20 mg/l of ibogaine, respectively) relative to the control (Table 1). Influence of the ascorbic acid in *in vitro* equipotent concentrations

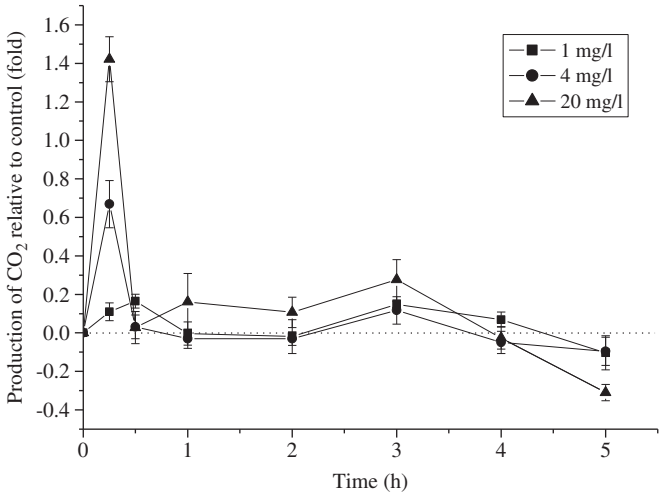

Fig. 1. Time dependent CO_2 production in yeast under 1, 4 and 20 mg/l of ibogaine in media. Results are expressed as the relative change in CO_2 production between exposed and control cells at each time point. They were collected from four independent cultures for each concentration. The data represent average values and standard errors.

Table 1
Concentrations of ibogaine in yeast cytosole after equilibrium, the influence of ibogaine at different concentrations on the total oxidative load and the influence of *in vitro* equipotent concentration of ascorbic acid are represented. The values represent averages and standard errors and are results of the experiment in triplicates.

Calculated ibogaine concentration [mg/l]	Ibogaine concentration in cytosol [mg/l]	Oxidative load ratio treated/control [%]	Ascorbic acid concentration [μM]	Oxidative load reduction by ascorbic acid
1	0.83 ± 0.03	76.26 ± 1.69	1	Non-significant
4	3.89 ± 0.06	76.67 ± 1.56	2	Non-significant
20	18.14 ± 0.34	43.45 ± 1.30	4	Non-significant

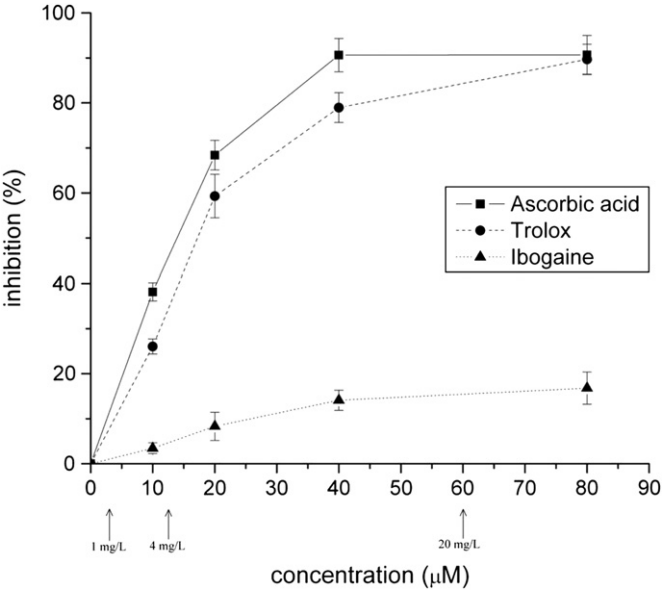

Fig. 2. *In vitro* anti-oxidant properties of ibogaine represented in molar concentrations. Results are expressed in percentage of DPPH reduction and were measured in triplicates. The bars represent averages and standard errors.

estimated in Fig. 2 to be 1, 2 and 4 μM was used as a positive control and no significant influence on oxidative load was found.

Ibogaine's intrinsic antioxidative potential was measured *in vitro* by DPPH test. Molar concentrations were used to compare with Trolox and ascorbic acid efficacy. No significant direct antioxidant properties of ibogaine were found in concentrations, relevant for experiment (Fig. 2).

The viability of yeast cells was examined by cell-membrane integrity test which excluded toxicity due to ibogaine presence at any concentration of concern (data not shown). Also, cell's morphology and growth after the treatment didn't show any deviations from control.

Ibogaine kinetics was examined in the yeast in phosphate buffer for different concentrations of ibogaine. Concentrations inside and outside the cells reached the balance in 2 h with a half of shift occurred in 15 min after beginning of the experiment. The results of measurements after equilibrium are shown in Table 1. Ibogaine as a highly lipid soluble molecule freely enters the cell and accumulates in the membranes causing a slight drop in concentration of water dissolved fraction. No noribogaine, a principal metabolite of ibogaine in humans was found neither in intracellular nor extracellular compartment at any time during the experiment.

4. Discussion

In our first work (Paškulin et al., 2006) induction of energy related enzymes in rat brain was demonstrated as a consequence of ibogaine administration. In our previous work (Paškulin et al., 2010) we have demonstrated similar results of ibogaine's influence on energy metabolism cluster in yeast *Saccharomyces cerevisiae*, while following the changes in ATP pool showed its transient reduction in a dose dependant manner. In the present experiment, the influence of ibogaine on metabolism was further studied on yeast in the stationary phase under aerobic conditions, this time by measuring the rate of CO_2 production and followed by search for energy consumers.

4.1. Energy metabolism acceleration

Transient oxidative energy metabolism acceleration was directly confirmed by increased CO_2 production after ibogaine exposure, in a dose dependant manner. Interestingly, this elevation is not permanent but shows rather interesting dynamics with biphasic elevation of CO_2 production, followed by the calming of catabolism at the end of the experiment.

Considering the fact that in spite of energy mobilization the ATP pool has been simultaneously decreased, the increased energy consumption as an early effect of ibogaine's presence was proven.

4.2. Possible energy consumers

4.2.1. Oxidative stress

Parallel to observation of the catabolism the level of oxidative stress as the sum of produced ROS was tracked under the same conditions. Surprisingly, we have observed that apart from undisputable increase in ROS formation due to stimulated ATP production (Halliwell and Gutteridge, 2007) there was a significant drop in the total oxidative load on the cell (Table 1). Since ibogaine doesn't show any significant *in vitro* antioxidant activity at the concentrations of concern and due to the failure of *in vitro* equipotent concentration of ascorbic acid to exert such effect *in vivo*, the impact on the physiological antioxidative systems must be responsible for such improvement, in a pro-antioxidant manner. Unlike the antioxidants that directly scavenge free radicals, pro-antioxidants act indirectly either by modulation of direct agents or by regulation of the biosynthesis of antioxidant proteins (Dinkova-Kostova and Talalay, 2008; Stevenson, 2012; Vertuani et al., 2004). Indeed, in our previous work (Paškulin et al., 2010) we have observed the 2,2 fold induction of Cu–Zn SOD enzyme expression after ibogaine treatment. Therefore, the reduction of oxidative load lowers energy expenses for cellular maintenance and saves the energy. This correlates with the later reduction of metabolic turnover as seen in Fig. 1.

4.2.2. Ibogaine kinetics

Energy consumption due to the ibogaine uptake cannot be responsible for energy load since active transport by specialized ATP coupled transporters is highly improbable at simple yeast model (Walker, 1998). Besides, it would show constant inward pumping effort opposing the escape of highly lipid soluble molecule (Maciulaitis et al., 2008) that would be presented as a constant rise in CO_2 production, rather than being expressed as biphasic production acceleration with latter inversion.

Redox and energy linked metabolism of ibogaine was checked regarding transformation to noribogaine, in mammals being catalyzed by CYP 450 enzyme reduction. This reaction is not possible since yeast does not posses CYP 450 system (Walker, 1998). Also, we have not found any measurable levels of noribogaine in the yeast cells, treated with ibogaine. Other possible degradation products were not undoubtedly excluded but any kind of energy coupled degradation would again manifest itself by constant CO_2 production elevation, prolonged far beyond our experiment until all ibogaine being metabolized.

4.2.3. Ibogaine toxicity

The ibogaine's toxicity with potential energy cost of cellular repairs was excluded by the test of cellular membrane's integrity and even further excluded by observations of normal growth and morphology after ibogaine exposure (data not shown). Also, literature denies antimicrobial activity of indole alkaloids from Apocynaceae family against yeast (Verpoorte et al., 1983).

Since transient, intermittent effort of coupled oxidative energy catabolism to compensate ATP pool diminution is not a permanent effect of ibogaine's presence, its toxicity or kinetics are not expected to be the subject of energy expenditure. Rather, a trigger mechanism is suspected where ibogaine serves as an elicitor of some finite energy consuming process. In our recent work (Paškulin et al., 2010) we have found induction of low abundance, functional protein fraction in yeast (including energy metabolism and antioxidative system enzymes in question), whose synthesis seems to be responsible for these energy expenditures. Deeper insight into the systems biology of complete proteome changes needs to be done for profound understanding of the ibogaine effect.

4.3. Acute effect

The ibogaine initiates the energy consuming process and manifestation of the effects depends on capability of catabolism to compensate the energy outputs in this dynamic equilibrium. This might be the case with low doses quickly gaining moderate improvement of physical and mental performance in a stimulant manner, while higher doses initially overcome cellular catabolism buffering capacity with energy flux being exclusively occupied with metabolic plasticity, not leaving much of free energy for physical activities. This puts the user in a period of lethargy under high ritual doses while full invigorating effect appears later (Fernandez, 1982).

Mind altering property of iboga might also be mediated by this mechanism of reduced energy availability (Magistretti, 2006).

Brain activity modulation due to interference of ibogaine in neurotransmitter release, action and reuptake extensively described in literature is undoubtedly involved in perception and cognitive shifts, but also reduced disposable energy has its implication. Brain cortex as energetically most demanding tissue and a site of cognition as well as psychological inhibitions can in case of ATP pool reduction move into a different mode of action. Decreased effectiveness of K/Na-ATPase due to acute lack of ATP might cause changes in electroencephalogram (EEG) patterns. This includes observed theta and delta trance state that precipitate subconscious psychological material into the awareness (Binienda et al., 2011; Strubelt and Maas, 2008).

Many factors influence the efficacy and safety of ibogaine use and so the justification of its use. Detoxification from drugs of abuse or any other recovery after illness is a restitution of physiological balance that by itself represents considerable energy load. Although ibogaine quickens such adaptation, such aid and its justification have its limits in terms of energy overload. Accelerated detoxification of severe addiction with the use of high ibogaine dose can overcome the body's buffering capacities and result in complications, so medical surveillance during such treatments is highly recommended.

4.4. After-effect

Under the cost of transitional energy expenditures ibogaine enables changes in proteome with the shift to a more economical and cytoprotective metabolic equilibrium. Besides, induced energy metabolism related enzymes serve as an extended energy source for a prolonged period of time. Resulting metabolic state is of special value in state of elevated energy demands under different stress in an adaptogen manner.

4.5. Ibogaine and anti-addiction effect

Tolerance is adaptation of an organism to the presence of drugs and their withdrawal causes the abstinence syndrome. Physical weakness with lack of will is recognized as one of symptoms. Besides subjective descriptions as "run out of gas", literature describes choking influence of diverse drugs of abuse on the energy metabolism (Chen et al., 2007; Hargreaves et al., 2009; Ryman and Walsh, 1951, 1952; Sadava et al., 1997). Reversibility of such changes is the platform for future anti-addiction treatments.

The prolonged anti-addiction effect of ibogaine at least partially consists of improved energy accessibility that can be considered as stabile metabolic shift in the epigenetic landscape (Huang et al., 2009; Waddington, 1957). While escaping the genetic determinism (Noble, 2006) such recognition of ibogaine as a causal remedy puts a question mark upon the definition of addiction as a chronic and relapsing disorder.

Nevertheless, full benefit of iboga use arises only from conjunction of its invigorating quality with the spiritually initiated intent for a life change—either initiating adulthood or quitting addiction (as if there was any difference…).

5. Conclusions

The increased energy consumption is confirmed to be the cause of acute energy depletion due to ibogaine. The proteome changes including induction of energy metabolism and antioxidative enzymes are responsible for initial energy expenditures. After the shift is accomplished the new metabolic equilibrium results in improved fitness.

As the dose distinguishes remedy from poison, the same is true for beneficial eustress influence of the adaptogen that can be overcame by adverse distress of metabolic overload. Special attention must be paid to pace at which the adaptation from one metabolic equilibrium to another is conducted.

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