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The effects of ibogaine on uterine redox homeostasis and contractility

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The ibogaine drug is originated from the rainforest shrub *Tabernanthe iboga*, which grows in West Africa. The tribes of the Gabon have used the iboga plant root bark for centuries as a stimulant, for medicinal purposes, and in rite of passage ceremonies. In the western world ibogaine is mostly known for its ability to inspire a sense of wellbeing both mentally and physically. Ibogaine has also been used for the treatment of substance abuse because it interrupts drug addiction, relieves withdrawal symptoms, and significantly decreases the desire for cocaine, heroin, alcohol and most other mind altering drugs. Now it is known that the pharmacology of ibogaine is quite complex and affects many different neurotransmitter systems simultaneously. Ibogaine binds to several types of receptors: 5-hydroxytryptamine (5-HT), opioid, nicotinic and N-methyl-D-aspartate (NMDA) receptors, dopaminergic and 5-HT transporters and monoamine oxidase enzyme (MAO) [1]. Although the mechanisms of ibogaine action in neural tissue are well studied, the effects on peripheral tissues are poorly understood.

Paskulin et al. have shown that ibogaine causes a sharp and transient fall in cellular ATP level in yeast, which was followed by an immediate increase in respiration and CO_2 production, in a time and concentration dependent manner [2,3]. Increased respiration leads to increase of ROS production and subsequent activation of antioxidant enzymes. These effects of ibogaine are not mediated by receptor binding and are not tissue and species specific [2,4]. It was previously shown that ibogaine-induced fall in cellular ATP level was caused by increased ATP consumption. The process in which the consumption of ATP is increased remains unclear. The proteome changes (induction of energy metabolism enzymes, antioxidant enzymes and numerous low abundance proteins) are responsible for at least a part of initial energy expenditures in ibogaine-treated yeast [2,5]. Study on human blood erythrocytes showed that ibogaine leads to release of ATP in the blood plasma [4].

Ibogaine doesn't have any significant in vitro antioxidant properties per se but it influences physiological oxidative stress defence system in pro-antioxidant manner [3,4].

In this study, we examined the effects of ibogaine on the model of the isolated rat uterus. Contractile tissues are sensitive to ATP levels and the depletion of energetics could lead to the impairment of regular rhythms and reversible relaxation. Extracellular ATP is known to stimulate uterine contractions in different species but the exact underlying mechanisms are poorly investigated. Furthermore, different contractile tissues, including uterus, are also sensitive to ROS, especially hydrogen peroxide (H_2O_2) [6]. Antioxidant enzyme cytosolic copper-zinc containing superoxide dismutase (SOD1) can also affect the contractility of uterine smooth muscles [7]. All these make the isolated contractile tissues a good model for examining the effects of ibogaine on both redox homeostasis and pharmacodinamics.

Unlike isolated arteries and ileum [8], the uterus may have a wide range of different types and intensities of contractile activity depending on the properties of the isotonic solution. This allows us to register not only the relaxant but also the stimulatory effect of the tested substance. The aim of this study was to investigate the effects of ibogaine on both contractile properties of uterus and redox homeostasis and explore the possible link between the two.

Overall, ibogaine treatment has altered redox homeostasis and affected contractile properties of uterus. Ibogaine had the opposite effects on spontaneously active rat uteri depending on the applied concentration. Lower concentrations increased force of contraction, amplitude, frequency and duration of individual contractions. Higher concentrations caused concentration dependent relaxation of spontaneously active uteri. On the other hand, when the uterus is contracting with a high intensity (when exposed to higher Ca^{2+} concentration) ibogaine showed only a relaxant effect.

The increase in uterine contractile activity after treatment with low doses of ibogaine could be partly attributed to possible increase in the extracellular concentration of ATP. However, the ATP leads only to a moderate increase in the intensity of uterine contractility, without affecting the character of contractions (i.e. their regularity), whereas ibogaine has a pronounced pace making effect.

Ibogaine also had a concentration dependant effect on the activity of antioxidant enzymes suggesting a vast, increase in cellular respiration and H_2O_2 level. Ibogaine mediated relaxation found in the present study can be attributed to the influence of H_2O_2. However, the other possible mechanisms of ibogaine induced smooth muscle relaxation cannot be eliminated, regarding to its wide range of interaction with different receptors and signal transduction pathways.

The results regarding energy metabolism and redox homeostasis are in accordance with the previous observations in different experimental models. Research on an isolated uterus has allowed us to further examine the mechanism of this phenomenon: whether the increase in the intensity of cellular respiration is the result of an increased contractile activity that is caused by ibogaine? Only partially, because ibogaine leads to an increase that is several times greater compared to the uterus with phasic contractile activity of maximal intensity,

induced by extracellular Ca^{2+}, indicating the existence of ibogaines tissue non-specific ways of energy metabolism induction.

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