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Krzysztof Borowiak[1], Anna Machoy-Mokrzyńska[2], Sławomir Majdanik[1], Piotr Waloszczyk[1], Magorzata Piasecka[3], Tomasz Janus[1], Ewa Jasionowicz-Piątek[1], Mirosław Parafiniuk[1]

PSILOCIN MULTIPLE INTAKE RESULTED AND IN CARDIOTOXIC EFFECTS

[1]Department of Forensic Medicine, [2]Department of Pharmacology,
[3]Department of Histology and Embriology, Pomeranian Medical University, Szczecin, Poland

ABSTRACT

Introduction: Natural hallucinogenic substances seem to be one of the addict agents most commonly used in European countries. The important source of those psychodysleptics may be a spreading growth of *Psilocybe genus* mushrooms.

Material and Methods: To verify a previously published hypothesis on cardiotoxicity of hallucinogens, the experimental study in the form of a three-month test on male Wistar rats was performed. The study groups received intraperitoneally psilocin (PSI) in a dose of 10 μg/kg body weight (b.w.) or beta-phenylethylamine (PEA) in a dose of 1 mg/kg b.w. dissolved in 5% ethanol every second day for 2 and 12 weeks. The control groups received 5% ethanol or 0.9% solution of NaCl for the same time periods. At the end of the experiment, biochemical blood parameters, ECG, and myocardial energetic status were examined, as well as histopathological and electron-microscopic examinations were performed. The decreased serum magnesium concentrations in the PSI-exposed animals were noted.

Results: The obtained results showed that the repeated (12 weeks) administration of PSI produces in rats ECG abnormalities in the form of tachycardia, myocardial ischaemia and aberrant intraventricular conduction. It was also stated that long-term exposure to PSI and PEA exerts a crucial effect on the energy heart muscle metabolism, which has been reflected in the complex changes in the myocardial profile of purine concentrations. These abnormalities corresponded with degenerative changes in cardiomyocyte mitochondria observed on histopathological and electron microscopy examinations.

Conclusions: The results of the study indicated a cardiotoxic effect of psilocin, manifested by functional and structural changes in cardiomyocytes and coronary arteries.

Key words: psilocin, phenylethylamine, hallucinogens, cardiology

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Address for correspondence:
Krzysztof S. Borowiak
Department of Forensic Medicine, Pomeranian Medical University
Powstańców Wlkp. 72, 70-111 Szczecin, Poland
Phone/fax: 48 91 466-15-79
E-mail: boroks@sci.pam.szczecin.pl

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INTRODUCTION

The main source of natural hallucinogens are mushrooms of the *Psilocybe* species (Magic cap). They contain both indole alkaloids (psilocybin, psilocin (PSI) and baeocistine) and biogenic amines (phenylethylamine) [1–4]. Despite their similar psychostimulative effect, the biochemical receptors of these compounds in the human central nervous system (CNS) are dissimilar. However, disorders inside and outside the CNS caused by the prolonged use or individual susceptibility are of no lesser importance. Several narcotics are capable of inducing acute myocardial ischaemia ultimately leading to myocardial infarction [5–8]. Until recently, it has been thought that the acute toxicity of PSI is low and thus the substance does not create a serious health hazard [1,9,10]. Symptoms observed after a single dose of *Psilocybe* mushrooms are generally limited to the CNS [2,11–13]. PSI also affects the autonomic nervous system, causing dryness in the mouth, tachycardia, hypotension, mydriasis or miosis, and loss of visual acuity [6,7,10,14]. All these symptoms are transient and amenable to physostigmine, disappearing without any permanent effects [15]. The general opinion of low toxicity and relative safety of natural hallucinogens has been questioned by researchers who described a case of acute myocardial infarction with arrhythmia in an 18-year-old male regularly consuming *Psilocybe semilanceata* products over a period of 30 days. Following this report, a hypothesis was advanced that the cardiotoxic properties of PSI result from coronary arteries spasm and accumulation of platelet aggregates, which additionally compromise blood flow. This combined effect is reflected by hypoxemia of cardiomyocytes mediated by serotonin and additionally by peripheral sympathomimetic activity [16]. Further research by other authors has corroborated the postulated mechanism, when it was demonstrated *in vitro* that serotonin impairs relaxation of coronary arteries in animal and human models [11,17,18]. Peripheral effects of narcotics on the cardiovascular system have been linked with their structural resemblance to biogenic amines [18–20]. The most probable mechanism tested so far involves coronary spasm, formation of platelet aggregates and thrombi in coronary arteries. Direct and indirect lesions to cardiomyocytes, related to increased oxygen consumption, accelerating atherogenesis and hypertrophic changes in the intimae were also considered [18].

The aim of our study was to verify a previously formulated hypotheses of cardiotoxicity of hallucinogens from *Psilocybe* muschrooms. The study protocol was approved by the local ethics commission.

MATERIAL AND METHODS

Subjects

The study was performed on 120 male Wistar rats, divided into six study groups, control and blank groups, during 3 months of spring. The animals were kept under controlled conditions and standard feed and water was given *ad libitum*, with a light/dark cycle of 12/12 h. The animals in the study groups, denoted PSI I, II, III (n = 15 in each), obtained intraperitoneally (i.p.), every second day, 1 mL of psilocin solution (Sigma, Germany) in 5% ethanol (10 μg/kg body weight (b.w.) corresponding to 1/100 LD_{50}). In the same way, the animals of the other study groups were injected 1 mL of beta-phenylethylamine (PEA) (Sigma, Germany) in 5% ethanol (1 mg/kg b.w.). These groups were denoted: PEA I, II, III (n = 15 in each). This time, it was the maximum dose noted in the black market tablets [21]. The rats in the control group (Ka, n = 15) received pure 5% water solution of ethanol, while the animals from the blank group (Ks, n = 15) were given natrium chloride (0.9% solution of NaCl). The doses were given until all the animals were sacrificed. The rats' autopsies were performed after 2, 8 and 12 weeks. The animals were anaesthetised with Ketamine (100 mg/kg b.w. i.p.). The hearts were isolated using tools cooled with liquid nitrogen. About 200-mg-myocardium samples from the ventricular area were collected in the plastic tubes and immediately frozen in liquid nitrogen. Next, two myocardium samples were collected in glass tubes with 10% formaline solution (histopathology) and 2.5% glutaric aldehyde (electron microscopy). Blood and urine samples were collected into separate glass tubes for biochemical assays.

Procedures

Serum concentrations of Ca^{++}, Li^{+}, K^{+} and Na^{+} were estimated with AVL 9140 electrolyte analyser equipment with ion selective electrodes. The method measurement ranges were 36–145 mmol/dm^{-3} for Na^{+}; 3.5–5.1 mmol/dm^{-3} for K^{+}; and 1.1~1.32 mmol/dm^{-3} for Ca^{++}. The concentrations of free and bound Mg^{++} were estimated for the mea-

surement range of 0.6–1.05 mmol/dm^{-3} with calorimetric Bio-Merieux test-kit.

In the morphologic and and biochemic analysis of blood, the number of red and white cells (RBC, WBC), platelets (PLT) and hemoglobin concentration (HGB) were determined with automatic measurement equipment of Olympus. The enzymatic activity of creatinine kinase (E.C. 2.7.3.2), lactate dehydrogenase (E.C 1.1.1.27), aspartate aminotransferase (E.C.2.6.1.1), alanine aminotransferase activity (E.C.2.6.1.2), creatinine kinase (E.C. 2.7.3.2), lactate dehydrogenase (E.C 1.1.1.27), aspartate aminotransferase (E.C.2.6.1.1), alanine aminotransferase (CPK, LDH, AspAT, ALAT) and biochemical (urea, creatinine) parameters were examined in serum with routine test-kits and Technicon Analyser.

Morphology of myocardium was performed in histological sections stained with hematoxylin and eosin, Van Gieson, and PAS.

Morphometric assessment of arteries in the myocardium was performed with Zeiss K 300 View Analyzer and Matrox Millenium graphic files. The following mathematic formulas were used for cross sections measurements of intramuscular arteries.

$$WO = (PERIM–PERIM\ F)/(PERIM\ F) \times 100\%,$$
$$WP = (AREA\ F–AREA)/(AREA) \times 100\%,$$

where:

WO — circuit factor, a percentage rate of the lumen circuit and external circumference of the artery;

WP — surface factor, a percentage rate of the artery lumen and surface of the artery wall;

PERIM — sum of the circuit of the artery lumen and external circumference;

PERIM F — external circuit length of arterial wall;

AREA F — surface of the artery wall and artery lumen;

AREA — surface of the artery wall.

In each heart, 5 cross sections of the arteries (comparable in size) were measured.

Ultrastructural malfunctions of miocytes and myocardium were estimated with transmission electron microscopy (JEM-1200 EX Japan, 80 kv).

All histological and ultrastructural findings were performed in accordance with the procedures described by Bancroft and Gamble [26].

All quantitative results are expressed as means ±SD. The statistical analysis of the results was performed with the Kruskal-Wallis test and/or Mann-Whitney U test.

RESULTS

Complete observations and precise results of ECG and energy status examinations were previously, separately published in two issues of the *Acta Toxicologica* [22,23]. The unpublished results of complement biochemical and morphological findings are presented below. The histological, morphometric, and electron microscopy procedures were performed on the animals exposed for 3 months to PSI and PEA.

In opposite to animals exposed to PEA, a significant ($p > 0.001$) increase in magnesium (Mg^{++}), decrease in calcium (Ca^{++}) concentration in serum, and the slight, but not statistically significant imbalance of all ions were noted in PSI-exposed animals as result of a 12-week exposure (Tab. 1).

Characteristic, consequent changes in blood morphology were observed in neither (PSI and PEA) group during the first two weeks of the experiment. However, a signifi-

Table 1. Blood ions concentration in the rats after a 12-week exposure to psilocin (PSI) and phenyletthylamine (PEA)

Parameter	PSI (n = 15)	PEA (n = 15)	Ka (n = 15)	Ks (n = 15)
Ca	0.66±0.064	0.62±0.028	0.67±0.524	1.17±0.329
Na	147.6±16.11	143.0±5.94	140.2±1.642	139.3±0.866
K	5.293±0.608	5.168±0.541	6.025±1.705	5.43±0.282
Cl	104±1.558	104.68±1.400	103.08±1.16	103±0.866
Mg	1.074±0.225	1.339±0.360	1.316±0.186	1.167±0.356

Ka — ethanol control group; Ks — blank group; Ca — calcium ion concentration — mmol/l; Na — sodium ion concentration — mmol/l; K — potassium ion concentration — mmol/l; Cl — chloride ion concentration — mmol/l; Mg — total magnesium concentration — mmol/l. All values are expressed as means ±SEM .

cant decrease in WBC number ($p < 0.01$) and HCT value as well as an increase in a percentage of neutrophiles ($p < 0.05$) were noted in the PSI group after 12 weeks of exposure. Simultaneously a slight decrease in RBC number ($p < 0.01$) resulted from the PEA exposure (Tab. 2).

The samples of heart muscle were examined histopathologically after 12 weeks of exposure. In the estimated cardiac slices collected in the PEA and PSI groups no characteristic fragmentation of separate cardiac fibres were expressed. However, in the PSI group

Table 2. Blood parameters in the rats exposed to psilocin (PSI) and phenylethylamine (PEA)

Parameter	PSI (n = 15)	PEA (n = 15)	Ka (n = 15)	Ks (n = 15)
WBC	2.847±0.861	4.52±1.299	3.92±1.61	4.25±1.01
NEU	31.57±7.31	31.71±10.09	28.00±8.50	22.6±7.86
LYMPH	54.26±7.73	54.16±10.94	58.15±8.50	62.72±8.03
MONO	7.48±1.91	7.68±2.23	7.99±3.85	7.09±2.73
EOS	4.52±2.03	4.47±1.69	4.09±1.84	5.58±2.98
BASO	1.87±0.92	1.96±0.59	1.73±0.94	2.00±0.71
RBC	8.27±0.40	7.90±0.36	8.60±0.95	8.74±0.60
HGB	8.93±0.24	8.58±0.40	9.20±0.78	9.56±0.59
HCT	0.747±0.02	0.71±0.029	0.77±0.06	0.79±0.048
PLT	1139.06±97.53	1151.93±131.28	1216.16±300.13	1211.66±153.41

Ka — ethanol control group; Ks — control blank group; WBC — white cells number x 103/cm^3; NEU — neutrofiles (%); LYMPH — limphocytes (%); MONO — monocytes (%); EOS — eozynofiles (%); HCT — hematocrit (%); BASO — bazofiles (%); RBC — red cells number x 106/cm^3; PLT — plate cells number x 103/cm^3; HGB — haemoglobin conc. (mg/dl).
All values are expressed as means ±SEM.

Table 3. The results of blood serum biochemical analysis in the rats after a 12-week exposure to psilocin (PSI) and phenylethylamine (PEA)

Parameter	PSI (n = 15)	PEA (n = 15)	Ka (n = 15)
CPK	2998.8±1004.21	2146.8±661.32	727.2±133.00
LDH	1897.0±314.31	2217.1±797.34	631.1±98.57
ASPAT	204.38±29.04	223.63±69.11	152.33±6.75
ALAT	100.07±37.00	185.2±110.59	52.66±1.35
UREA	38.8±1.37	40.0±3.73	42.7±1.37
CREAT	0.486±0.01	0.443±0.04	0.44±0.01

Ka — ethanol control group; CPK — creatinine kinase activity IU (E.C. 2.7.3.2); LDH — lactate dehydrogenase activity IU (E.C 1.1.1.27); ASPAT — aspartate aminotransferase activity IU (E.C.2.6.1.1); ALAT — alanine aminotransferase activity IU (E.C.2.6.1.2); UREA — urea concentration — mg/dl; CREAT — creatinine concentration — mg/dl.
Values are means ±SEM.

Biochemical assays revealed a temporary (after 2 weeks of exposure), significant increase in serum CPK ($p < 0.05$), LDH ($p < 0.01$), and AspAT ($p < 0.001$) activity in both group (PSI and PEA). Those increased levels maintained for a couple of weeks in the PSI group, while the noticeable deficiency in their activity was noted after 12 weeks of exposure (Tab. 3).

the process off enhanced connective tissue, increased thickness and fibrosis of the walls of arteries (Van Gieson), connected with growing number of fibroblast cells, was noted (Fig. 1).

The morphometric assessment of chronic morphological changes was performed to standardise the histopathological results. The wall area and circumference

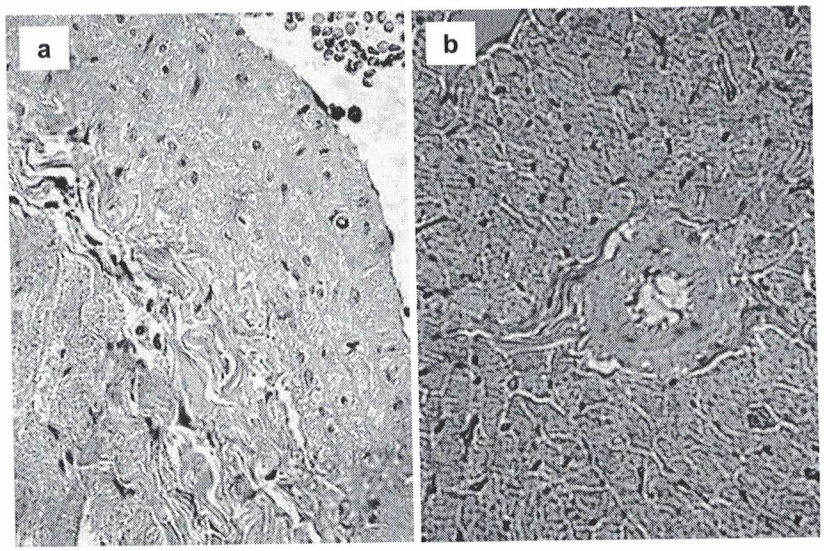

Fig. 1. Subendocardiac (a) and perivascular (b) accumulation of connective tissues after a 12-week exposure to psilocin (PSI) (Van Gieson staining, × 400).

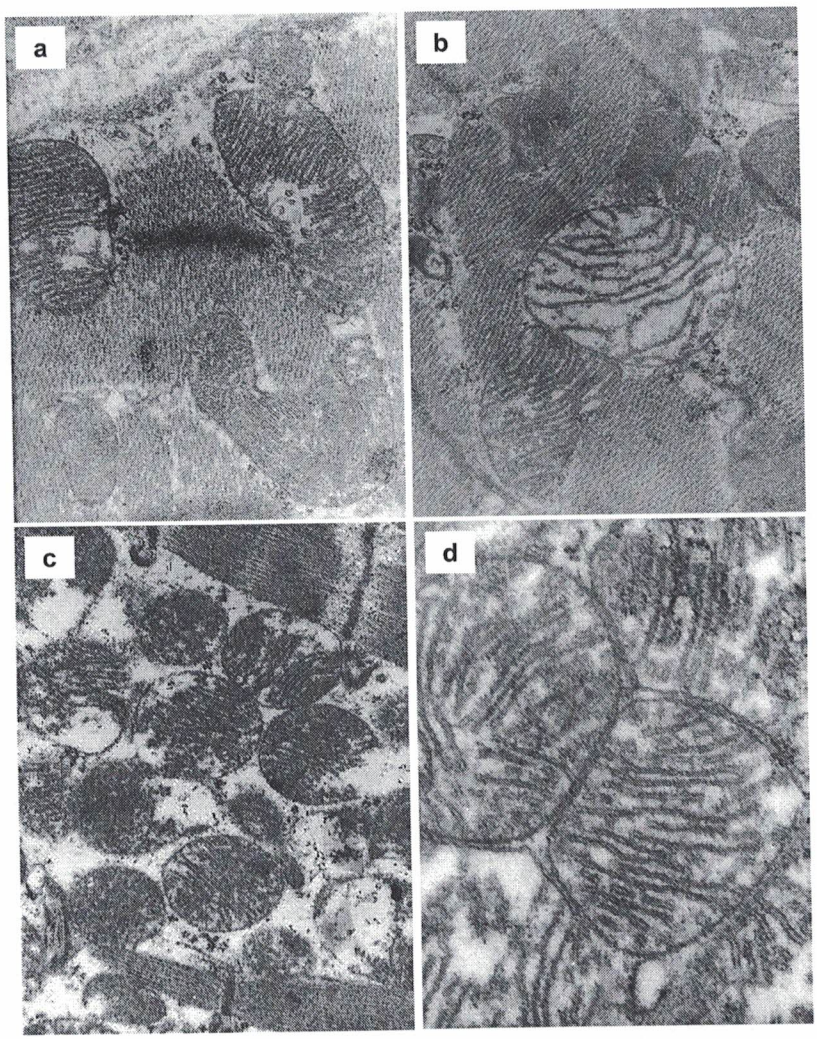

Fig. 2. An advanced damage to mitochondria by cardiomyocytes in the psilocin (PSI) group. Expressed fragmentation and discerption of mitochondrial membranes and decreased matrix density of mitochondria (3a,b × 30 000; 3c × 25 000, 3d × 65 000).

Table 4. Morphometric parameters of the cardiac cross-section arteries in the rats after a 12-week exposure to psilocin (PSI) and phenylethyulamine (PEA)

Parameter	PSI (n = 15)	PEA (n = 15)	Ka (n = 15)	Ks (n = 15)
WP	0.404±0.046	0.385±0.031	0.385±0.046	0.437±0.046
WO	0.433±0.163	0.515±0.016	0.48±0.032	0.491±0.200

Ka — ethanol control group; Ks — blank group; WP — surface factor; WO — circumference factor. All values are expressed as means ±SEM.

of coronary vessels were measured. The value of circuit factor (WO) seems to be the most characteristic differentiate parameter. The significantly increased value of WO in the PSI group, compared with Ka, Ks and PEA groups of animals, was noted (Tab. 4).

Chronic changes of cytoplasm organelles were observed with an electron microscopy technique. A distinctly higher number of the damaged mitochondria in animals exposed to PSI in comparison with the PEA, Ka, and Ks groups was noted on the ultrastructural examination. Numerous areas with lower electron density, narrow number of cristae and lamellar structures were observed. Fractures and discerptions of mitochondrial crests in a number of cells and areas with declined electron density were also expressed (Fig. 2).

DISSCUSSION

Hallucinogens are notable chiefly for their immediate psychomimetic effects [6,11]. One of their main natural sources are mushrooms of the *Psilocybe* species [1,4]. Hallucinogenic substances are indole (serotonin-like) or phenylethylamine derivatives [4,7]. Until recently, investigations focused on psilocin and its precursor — psilocybin. Both substances have been attributed to psychodysleptic properties [12,13]. In the second half of the 1990s, attention was drawn to the role of phenylethylamine in the toxicity of *Psilocybe* mushrooms [3,7]. The activity of PEA principally targeting the central nervous system has been related to its structural resemblance to dopamine and noradrenaline. PEA enhances the release of endogenous dopamine, exhibiting at the same time direct sympaticomimetic properties and apparently acts as a CNS transmitter [24]. Biochemical reactions with the participation of 2-phenylethylamine slightly differ from the metabolic pathways of catecholamines [21,24,25]. As discussed earlier, intake of *Psilocybe* mushrooms was considered to be a relatively safe form of addiction. Psilocin is well known as a typical blocker of serotonin receptors. Numerous reports concentrated on the transient psychoses, leaving aside the possibility of somatic abnormalities [2,12,13]. It was not until the second half of the 1990s when the first reports on cardiotoxic action of natural hallucinogens appeared [3,12,16]. Thus to verify a previously made hypothesis of cardiotoxicity of hallucinogens from Psilocybe mushrooms [16] and to make at attempt at explaining the cardiac effects and ultrastructural changes with the multi-technique assessment a three-month test was performed. The presented results bring about new relevant arguments against a common opinion on the safety of this abused fashion and low toxicity of hallucinogen repeated intake.

Severe abnormalities like tachycardia, signs of myocardial ischaemia, and disorders of intraventricular conduction often terminating in right bundle branch block were observed on electrophysiological examination. Changes observed in the ECG pattern (elevation of ST segment) are often characteristic of coronary vasospasm. Those ECG disorders were well linked and time-synchronised with the increase of cardiac profile enzymes (CPK, LDH, AspAT), electrolyte imbalance (Ca, Mg) and heart muscle energy depletion. Changes in purine concentrations reflect an increase in the myocardium energy charge rise along with duration of exposure to PSI and PEA.

The observed physiological and biochemical disturbances mostly well corresponded with structural changes noted in the histopathological findings. Our morphometric findings in animals exposed to PSI were suggestive of vascular lesions in the form of subendocardial fibrosis and thickening of coronary arteries. The perivascular fibrosis with proliferation of fibroblasts and connective tissue growth was also demonstrated. The severe ultrastructural, mitochondrial damages to cardiomyocytes

excellently reflected the previously described impairment of energy consumption [23]. It should be expected that cardiovascular abnormalities noted in PSI-exposed animals were mediated by serotonin receptors [9]. An interesting concept relates to the link between platelet serotonin and pathogenesis of ischaemic heart disease. Opinions on the role of 5-HT in the regulation of the cardiovascular system remain equivocal [3,10,15], probably because of the multifarious action of serotonin, depending on the receptor type. This amine is capable of eliciting constriction or relaxation of large arteries and arterioles at the same time and the final result will depend on the relative strength of one effect over the other [20].

Phenylethylamine proved to be much less active as could be expected of an endogenous analogue of amphetamine. Based on our own results and the literature data, it can be concluded that PEA exerts a stronger but shorter and non-fixed effects on the cardiovascular system during subacute intoxication [3,16]. Transient tachycardia was the main finding in the early phase of the experiment. Elevation of ST segment and aberrant intraventricular conduction were rare. Neither distinct, durable abnormalities in the biochemical parameters nor pathomorphological changes were observed after 12 weeks of exposure. Apparently the cardiovascular system retains a significant capacity for the adaptation to PEA [3,21,25]. The presented results demonstrated that psilocin may have manifold cardiotoxic properties at relatively low doses, when it is taken regularly over a period of several weeks. This field of research has recently gained much importance due to a growing number of PSI users, which indicates the necessity to continue investigations on this issue.

CONCLUSSION

1. The cardiotoxic effects of psilocin was proved by noted functional and structural changes in cardiomyocytes as well as in coronary arteries.
2. Phenylethylamine revealed low toxicity on the cardiovascular system and the observed effects may be considered as functional and reversible.
3. The possibility of cardiac dysfunctions and structural damages resulted from regular hallucinogenic mushroom intake must be respected.

K. Borowiak, A. Machoy-Mokrzyńska, S. Majdanik, P. Waloszczyk, M. Piasecka, T. Janus, E. Jasionowicz-Piątek, M. Parafiniuk

WIELOKROTNE PRZYJMOWANIE PSYLOCYNY MOŻE WYWOŁAĆ EFEKTY KARDIOTOKSYCZNE

Streszczenie

Naturalne związki halucynogenne należą w ostatnich latach, w większości krajów europejskich, do najpopularniejszych preparatów odurzających. Ważnym źródłem tych związków są powszechnie występujące w lasach Europy grzyby z rodzaju *Psilocybe*. Podjęto próbę weryfikacji hipotezy, opublikowanej w 1998 r., wskazującej na potencjalną możliwość wywołania przez te związki efektów kardiotoksycznych. W tym celu przeprowadzono 3-miesięczne badania w warunkach eksperymentalnych na szczurach z wykorzystaniem kilku technik badawczych pozwalających na ocenę fizjologicznych i morfologicznych efektów działania badanych substancji.

Zwierzęta z grup badanych co 2 dni przez 3 miesiące otrzymywały dootrzewnowo psylocynę w dawce 10 ug/ml m.c. (grupy PSI) lub fenyloetyloaminę w dawce 1 mg/kg m.c. (grupy PEA) zawieszone w 5% etanolu. Zwierzęta z grup kontrolnych otrzymywały 5% etanol (Ka) lub sól fizjologiczną (Ks).

Jak przedstawiono we wcześniejszych doniesieniach, otrzymane rezultaty wykazały, że 12-tygodniowe, regularne przyjmowanie psylocyny skutkuje zaburzeniami funkcjonalnymi pracy serca (badania EKG, biochemiczne, ocena stanu energetycznego mięśnia sercowego). Z tymi wynikami znakomicie korespondują rezultaty badań morfologicznych, morfometrycznych i ultrastrukturalnych, które ilustrowały zmiany degeneracyjne mitochondriów w kardiomiocytach oraz zmiany typu włóknienia w ścianie naczyń wieńcowych.

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