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Effects of helium-oxygen and hyperbaric helium-oxygen environment on drug-metabolizing enzyme activity in rat liver

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Geiger JD, Akers TK, Parmar SS. Effects of helium-oxygen and hyperbaric helium-oxygen environment on drug-metabolizing enzyme activity in rat liver. Undersea Biomed Res 1983; 10(4):321–329.—The effects of room-air normoxic (22°C ± 1°C), 1.2-ATA He-O_2 (400 mmHg P_{O_2}, 29.0°C ± 1°C), and 21-ATA He-O_2 (400 mmHg P_{O_2}, 32.5°C ± 1°C) environments were investigated on the activity of drug-metabolizing enzyme systems in rat liver, as monitored by *O*-dealkylation and *N*-dealkylation reactions. Continuous exposure of rats to both He-O_2 environments for 12 days significantly increased the in vitro activity of drug-metabolizing enzymes in liver preparations. The increase in the in vitro *O*-dealkylation of *p*-nitroanisole based on product formed · mg protein^{-1} · 20 min^{-1} was 32.2% ($P < 0.05$) between normoxic animals and those exposed to 1.2 ATA He-O_2, and 24.4% ($P < 0.01$) in animals exposed to between 1.2 and 21 ATA He-O_2. A significant increase of 48.8% ($P < 0.001$) was noted between normoxic animals and those exposed to 21 ATA He-O_2. Similar differences were noted if the data were expressed on the basis of 200 mg liver wet wt. The *N*-dealkylation of morphine based on product formed · mg protein^{-1} · 20 min^{-1} was significantly increased between animals kept at normoxic and at 1.2-ATA He-O_2 conditions (17.6%, $P < 0.05$) and between animals kept at normoxic and at 21 ATA He-O_2 conditions (28.2%, $P < 0.05$). No significant differences for *N*-dealkylation of morphine were noted between animal groups at 1.2 and those at 21 ATA He-O_2 nor between any animal groups for *N*-dealkylation of cocaine.

hyperbaric pressure
drug metabolism
enzyme activity
helium
rats
morphine
cocaine

Navy, industrial, and recreational divers breathe mainly helium-oxygen mixtures during deep saturation dives. Nitrogen is added in many instances to protect against the high pressure nervous syndrome (1). However, the optimal oxygen tension in these breathing mixtures appears unresolved (2). Exposure of divers to hyperbaric pressures for extended periods of time may necessitate administration of pharmacological agents during or directly following this exposure. It is therefore important to characterize the various pharmacokinetic parameters possibly affected by such environmental exposure; among these parameters is the activity of drug-metabolizing enzymes in the liver.

Alterations in the activity of drug-metabolizing enzymes and other enzyme systems have been observed with changes in atmospheric pressure and respiratory oxygen (3–5). Geiger et al. (6) reported that significant increases in *O*-dealkylation of *p*-nitroanisole was observed in rat liver preparations obtained from animals exposed to 21 ATA He-O_2 (200 mmHg Po_2) for from 8 to 84 continuous days when they were compared to room-air normoxic control animals; *N*-demethylation rates of cocaine and morphine were not similarly affected. Tofano et al. (7) noted that exposure of rats to an 11-ATA He-O_2 environment for only 4 h was sufficient to cause significant induction of *N*-demethylating drug-metabolizing enzyme activity for morphine. This induction of drug-metabolizing enzyme activity was not observed when isolated rat liver parenchymal and nonparenchymal cells were incubated with several different drugs at 70 ATA in an unspecified gaseous environment (8).

This study was conducted to evaluate further whether exposure of rats for 12 consecutive days to room-air normoxic, 1.2 ATA He-O_2 (400 mmHg Po_2), or 21 ATA He-O_2 (400 mmHg Po_2) conditions affected drug-metabolizing enzyme activity.

MATERIALS AND METHODS

The experimental facility in the high pressure laboratory at the University of North Dakota consisted of two main spheres (diam 215-cm) connected by a 60-cm gate valve and seven subchambers (102-cm long 46-cm in diam) connected to each sphere by 46-cm gate valves. Each main sphere had a centrally located turntable upon which an electrically controlled tractor was mounted. This tractor was capable of entering the subchambers individually for the purpose of removing and relocating racks of animals and supplying food and water. Three subchambers were utilized for this study. During the experiment animals were transferred to the central sphere and the subchambers were isolated (by closing the 46-cm gate valve), decompressed, cleaned, replenished with food and water, and recompressed. Animals were then moved back into the replenished subchambers.

Twenty-four male Sprague-Dawley albino rats, ranging in weight from 90 to 145 g, were maintained on Purina lab chow. They received water ad libitum from time of arrival to termination. Two animals were placed in each cage and four cages were fitted on a rack. The rack containing 8 experimental animals was placed in the subchamber, and the animals were kept in an He-O_2 environment at 21 ATA (294 psig) with a Po_2 of 400 mmHg. For the full period of these experiments the animals were maintained at a temperature of 32.5°C ± 1°C in accordance with the results of Stetzner and DeBoer (9). An identical rack housing 8 animals was placed in another subchamber where conditions of 1.2 ATA He-O_2 with Po_2 of 400 mmHg at 29.0°C ± 1°C were maintained. This slight positive pressure was necessary to maintain adequate gas circulation. The third rack of 8 animals was placed in a mock chamber that was maintained at ambient temperature (22°C ± 1°C) and normoxic conditions. All animals were supplied fresh food and water every 48 h for 12 days.

After the subchamber was flushed with the He-O_2 mixture, the animals were compressed to 21 ATA in 2 h (5 psig/min). Compression was controlled by an IBM 1800 computer. The internal lighting of the subchamber was maintained on a 12-h schedule throughout the experiment. The compressed He-O_2 mixture was continuously circulated through the subchambers at a rate of 142 liters/min with the humidity kept below 30%. Once during every 24-h period the He-O_2 mixture was circulated for 8 h through pressurized molecular sieve towers (Vapoilsorb and Molecular Sieve #544; C. M. Kemp Mfg. Co., Glen Burnie, MD). This treatment served to remove the accumulated ammonia and carbon dioxide; levels of ammonia and carbon dioxide

were not measured in these studies. After 12 days the subchamber containing the experimental animals was isolated, and a 6.5-h staged decompression controlled by the IBM 1800 computer ensued according to a schedule reported by Bares (10).

Rat liver enzyme preparations

Each control and experimental animal was weighed, anesthetized with ether, and exsanguinated by heart puncture through the body wall. The livers were immediately removed, weighed, and homogenized individually, without perfusion, in ice-cold 1.15% potassium chloride (wt/vol) in a ratio of 1:4 (wt/vol), using a Potter-Elvehjem homogenizer (Wheaton Sci., Des Plaines, IL). The homogenates were centrifuged separately at 9000 *g* for 20 min at 4°C, and the supernatant solutions were used as the source of the rat liver drug-metabolizing enzyme preparations (11). Approximately 0.5 g of wet liver were placed in aluminum weighing pans for drying and later determination of ratios of wet to dry liver.

The determination of activity of rat liver drug-metabolizing enzymes was performed essentially as described by Mazel (12). The reaction mixture in a total volume of 3 ml consisted of phosphate buffer (0.1 M, pH 7.4), 10 μmol of glucose-6-phosphate, 0.48 μmol of nicotinamide adenine dinucleotide phosphate (NADP), 15 μmol $MgCl_2$, 20 μmol of nicotinamide, 10 μmol of various substrates, and 1 ml of 9000-*g* supernatant fraction equivalent to 200 mg wet wt of the liver. The enzyme preparations were incubated at 37°C, oxygen being used as the gas phase in the Dubnoff metabolic shaker (Precision Sci. Co., Chicago, IL). The reaction was started by the addition of suitable substrate, and the reaction was further incubated for 20 min. The *O*-dealkylation reaction, in which *p*-nitroanisole was used as the substrate, was stopped by the addition of 1 ml of 20% trichloroacetic acid solution (wt/vol), and the activity of liver drug-metabolizing enzymes was determined by using colorimetric technique to estimate the amount of the product (*p*-nitrophenol) formed. In the experiments for the determination of the activity of drug-metabolizing enzymes during *N*-dealkylation reactions, 40 μmol of semicarbazide hydrochloride were added to the reaction mixtures to bind the formaldehyde produced during oxidation. The reaction was stopped by the addition of 2 ml of Nash reagent (20% ammonium acetate containing 0.4 ml acetylacetone), and the mixture was heated in a boiling water bath for 10 min to precipitate the proteins. The formaldehyde produced was measured by use of the colorimetric technique. The activity of the drug-metabolizing enzymes was calculated on the basis of nmol of product formed per 200 mg of wet liver wt per 20 min, nmol of product formed per mg of protein per 20 min, and nmol of product formed per 20 mg of dry liver wt per 20 min. Mean values for each animal were obtained through triplicate experiments.

Total proteins of the various enzyme preparations were determined by the method of Stevens (13), specifically for use with the Technicon Auto-Analyzer (Technicon Instruments Corp., Tarrytown, NY). Data were subjected to one-way analysis of variance, and Dunnett's multiple comparison tests or Students' *t* test was used for determination of statistical significance. Significance was considered at the 95% confidence level and the results are reported with respective *P* values.

RESULTS

General observations

The present study demonstrated that rats continuously exposed to room air (normoxic), to 1.2 ATA He-O_2 (400 mmHg P_{O_2}), and to 21 ATA He-O_2 (400 mmHg P_{O_2}) survived and grew

without any mortality attributable to the hyperbaric environment. The body weights of the three groups of animals are shown in Table 1. The room-air normoxic animals grew the fastest, gaining 73.6 ± 5.9 g in 12 days. The animals exposed to 1.2 ATA He-O_2 and to 21 ATA He-O_2 gained 49.0 ± 3.3 and 39.8 ± 2.8 g, respectively. The growth rate differences between the normoxic and the 1.2- and the 21-ATA He-O_2 animals were significant ($P < 0.01$); however, the differences between the 1.2-ATA and the 21-ATA He-O_2 animals were not.

In Table 2 wet and dry weights of liver, ratios of wet liver to dry liver (wet/dry ratios), and concentrations of drug-metabolizing enzyme proteins in rat liver are listed. The wet/dry ratios from normoxic, 1.2-ATA He-O_2, and 21-ATA He-O_2 animals were 3.53 ± 0.05, 3.41 ± 0.07, and 4.01 ± 0.12, respectively. The differences between the 1.2-ATA He-O_2 and the 21-ATA He-O_2 wet/dry ratios and between normoxic and 21-ATA He-O_2 wet/dry ratios were statistically significant ($P < 0.01$). The enzyme protein concentrations for these animals were 2.35 ± 0.13, 2.36 ± 0.08, and 2.39 ± 0.13 mg/20 mg wet wt liver, respectively. None of these differences were statistically significant.

Activity of drug-metabolizing enzymes

Exposure of rats to both a 1.2-ATA He-O_2 and a 21-ATA He-O_2 environment caused significant increases in the activity of rat liver drug-metabolizing enzymes during *O*-dealkyla-

TABLE 1

BODY WEIGHTS OF RATS EXPOSED TO THREE GASEOUS ENVIRONMENTS FOR 12 DAYS

Environment	No. of Animals	Body Weights, g		
		Initial*	Final**	Increase
Normoxic	8	103.6 ± 3.2	177.2 ± 4.9	73.6 ± 5.9
1.2 ATA He-O_2	7	139.9 ± 2.0†	189.0 ± 4.1	49.0 ± 3.3†
21 ATA He-O_2	8	137.4 ± 2.4‡	177.2 ± 3.2	39.8 ± 2.8‡

Values represent mean values ± SE. *Initial body weights noted just prior to placement in environmental chambers. **Final weights recorded at time of death. †$P < 0.01$ Normoxic vs. 1.2-ATA He-O_2 animals. ‡$P < 0.01$ Normoxic vs. 21-ATA He-O_2 animals.

TABLE 2

EFFECTS ON LIVER PARAMETERS OF RATS EXPOSED FOR 12 DAYS TO GASEOUS ENVIRONMENT

Environment	No. of Animals	Wet Weight, g	Dry Weight, g	Wet/Dry Ratio	Enzyme Protein, mg/20 mg
Control Animals					
Normoxic	8	0.44 ± 0.06	0.12 ± 0.02	3.53 ± 0.05	2.35 ± 0.13
1.2 ATA He-O_2	7	0.45 ± 0.05	0.13 ± 0.01	3.41 ± 0.07	2.36 ± 0.08
Experimental Animals					
21 ATA He-O_2	8	0.38 ± 0.02	0.10 ± 0.01	4.01 ± 0.12*,**	2.39 ± 0.13

Values represent mean values ± SE. Procedures for determination of liver weights and enzyme proteins are described in text. *$P < 0.01$ Normoxic vs. 21-ATA He-O_2 animals. **$P < 0.01$ 1.2-ATA He-O_2 vs. 21-ATA He-O_2 animals.

tion of *p*-nitroanisole. Table 3 shows that when the activity is calculated on the basis of nmol product formed · 200 mg^{-1} wet wt · 20 min^{-1} the enzyme activity increased from 49.6 ± 5.1 to 72.0 ± 4.6 to 98.2 ± 7.1 for normoxic, 1.2-ATA He-O_2, and 21-ATA He-O_2 animals, respectively. The 31.1% increase between normoxic and 1.2-ATA He-O_2 animals was significant at the $P < 0.05$ level. The 26.7% increase between 1.2-ATA He-O_2 and 21-ATA He-O_2 animals was statistically significant ($P < 0.01$), as well as the 49.5% increase between normoxic and 21-ATA He-O_2 animals ($P < 0.001$). Such an increase was also reflected when the enzyme activity was expressed as mg protein · 20 min^{-1}. The 32.2% increase between preparations from normoxic (2.1 ± 0.2) and 1.2-ATA He-O_2 (3.1 ± 0.3) control animals was statistically different ($P < 0.05$), as well as the 24.4% increase observed between the 1.2-ATA He-O_2 and 21-ATA He-O_2 (4.1 ± 0.3) animal preparations ($P < 0.01$). The 48.8% increase between preparations from normoxic and 21-ATA He-O_2 animals was also significant ($P < 0.001$).

The effects of these environments on the activity of rat liver drug-metabolizing enzymes during *N*-dealkylation of morphine are recorded in Table 4. Enzyme activity, calculated on the basis of both 200 mg liver wet wt and mg protein, showed a significant increase of 17.4% ($P < 0.05$) and 17.6% ($P < 0.05$) between room-air and 1.2-ATA He-O_2 control animals,

TABLE 3

ACTIVITY OF RAT LIVER DRUG-METABOLIZING ENZYMES DURING *O*-DEALKYLATION OF *P*-NITROANISOLE AFTER CONTINUOUS EXPOSURE TO GASEOUS ENVIRONMENTS FOR 12 DAYS

Environment	No. of Animals	Drug Metabolizing Enzyme Activity, Product Formed/20 min	
		200 mg wet wt	mg protein
Normoxic	8	49.6 ± 5.1	2.1 ± 0.2
1.2 ATA He-O_2	7	72.0 ± 4.6*	3.1 ± 0.3*
21 ATA He-O_2	8	98.2 ± 7.1**,†	4.1 ± 0.3**,†

Each experiment was performed in triplicate and values represent mean values ± SE. Procedures for determination of drug metabolizing enzyme activity are described in the text. *$P < 0.05$ Normoxic vs. 1.2-ATA He-O_2 animals. **$P < 0.001$ Normoxic vs. 21-ATA He-O_2 animals. †$P < 0.01$ 1.2-ATA He-O_2 vs. 21-ATA He-O_2 animals.

TABLE 4

ACTIVITY OF RAT LIVER DRUG-METABOLIZING ENZYMES DURING *N*-DEALKYLATION OF MORPHINE AFTER CONTINUOUS EXPOSURE TO GASEOUS ENVIRONMENTS FOR 12 DAYS

Environment	No. of Animals	Drug-Metabolizing Enzyme Activity*, nmol	
		200 mg wet wt	mg protein
Normoxic	8	128.7 ± 9.2	5.6 ± 0.3
1.2 ATA He-O_2	7	155.9 ± 7.9**	6.8 ± 0.3**
21 ATA He-O_2	8	182.9 ± 11.26†	7.8 ± 0.6‡

Each experiment was performed in triplicate and values represent mean values ± SE. Procedures for determination of drug metabolizing enzyme activity are described in text. *Activity expressed as nmol product formed · 200 mg wet wt^{-1} · 20 min^{-1} and as nmol product formed · mg $protein^{-1}$ · 20 min^{-1}. **$P < 0.05$ Normoxic vs. 1.2-ATA He-O_2 animals. †$P < 0.05$ Normoxic vs. 21-ATA He-O_2 animals. ‡$P < 0.05$ Normoxic vs. 21-ATA He-O_2 animals.

respectively. Nonsignificant increases of 14.8% and 12.8% were noted between 1.2-ATA He-O_2 and 21-ATA He-O_2 animals when enzyme activity was calculated on the basis of 200 mg wet wt or of mg protein. However, significant differences of 29.6% ($P < 0.01$) and 28.2% ($P < 0.05$) were noted between normoxic and 21-ATA He-O_2 animals.

Results recorded in Table 5 report the effects of 12 days of exposure of animals to these environments on the activity of rat liver drug-metabolizing enzymes during *N*-dealkylation of cocaine. Enzyme activity based on 200 mg wet wt demonstrated a nonsignificant increase of 18.1% and 5.3% between room-air and 1.2-ATA He-O_2 animals and between 1.2-ATA He-O_2 and 21-ATA He-O_2 animals, respectively. Similar nonsignificant increases of 16.2% and 1.4% were observed when the enzyme activity was expressed in terms of milligrams of protein. Nonsignificant differences were also observed between normoxic and 21-ATA He-O_2 animals when enzyme activity was expressed either on the basis of 200 mg wet wt or milligrams of protein.

DISCUSSION

The rats exposed continuously to an environment of 21 ATA He-O_2 (400 mmHg P_{O_2}) were capable of life, growth, and development. Earlier studies have confirmed that rats exposed to hyperbaric conditions maintain normal skeletal growth and kidney function (2) even in hyperbaric environment with elevated oxygen. The present study has demonstrated that animals kept at room pressure normoxic conditions grew faster than the rats exposed to either 1.2-ATA He-O_2 or 21-ATA He-O_2 (400 mmHg P_{O_2}). It is important to note, however, that during the 12-day period of these experiments no difference in growth rate was noted between groups of animals kept at either 1.2 ATA or 21 ATA He-O_2 (400 mmHg P_{O_2}).

Hyperbaric diuresis in animals (2, 14) and human subjects (15) prompted us to check ratios of liver wet and dry weights. A significant increase ($P < 0.05$) in the ratio was observed in animals exposed to 21 ATA He-O_2 when compared with both room-air and 1.2-ATA He-O_2 control animals. Such a change is indicative of shifts in water balance within the test animals due to hyperbaric He-O_2 and not He-O_2 alone. The protein concentrations in the liver preparations used for drug-metabolizing enzyme activity were not significantly altered between any of the animal groups. These results are at variance with some earlier reported work showing significant reductions in protein concentrations in isolated liver preparations taken from normoxic and 21-ATA He-O_2 (200 mmHg P_{O_2}) animals after 22 days and 84 days, respectively (6).

TABLE 5

ACTIVITY OF RAT LIVER DRUG-METABOLIZING ENZYMES DURING *N*-DEALKYLATION OF COCAINE AFTER CONTINUOUS EXPOSURE TO GASEOUS ENVIRONMENTS FOR 12 DAYS

Environment	No. of Animals	Drug-Metabolizing Enzyme Activity*	
		200 mg wet wt	mg protein
Normoxic	8	127.7 ± 13.2	5.7 ± 0.7
1.2 ATA He-O_2	7	155.9 ± 8.1	6.8 ± 0.3
21 ATA He-O_2	8	164.6 ± 13.8	6.9 ± 0.6

Each experiment was performed in triplicate and values represent mean values ± SE. Procedures for determination of drug metabolizing enzyme activity are described in text. *Activity expressed as nmol product formed · 200 mg wet wt^{-1} · 20 min^{-1} and as nmol product formed · mg $protein^{-1}$ · 20 min^{-1}.

These apparent discrepancies are probably due to the shorter exposure time (12 days) in the present experiments.

Significant increases ($P < 0.05$) in the *O*-dealkylation of *p*-nitroanisole were noted in liver preparation taken from rats exposed to 1.2 ATA He-O_2 (400 mmHg Po_2) environment for 12 days when compared to that from room-air control animals. Additionally, significant differences ($P < 0.01$) were noted between 1.2-ATA and 21-ATA He-O_2 animals. These significant differences were noted whether the enzyme activity was based on 200 mg liver wet wt, 200 mg liver dry wt (data not included), or on milligrams of protein. Previous work reported similar increases between normoxic and 21-ATA He-O_2 (200 mmHg Po_2) animals (6).

The activity of drug-metabolizing enzymes during *N*-dealkylation of morphine was significantly increased ($P < 0.05$) between normoxic and 1.2 ATA He-O_2 animals. Significant differences were also seen between normoxic and 21-ATA He-O_2 animals. These significant differences were observed whether the enzyme activity was calculated on the basis of 200 mg liver wet wt, 200 mg liver dry wt (data not included), or milligrams of protein. Nonsignificant increases were noted between 1.2 ATA He-O_2 and 21 ATA He-O_2 animals. These findings are in partial agreement with Tofano et al. (7) and Geiger et al. (6), where significant and nonsignificant increases in *N*-dealkylation of morphine were reported for 21-ATA He-O_2 exposure for 4 h or 8–84 days, respectively.

No significant differences between any of the groups of animals in this study were noted for *N*-dealkylation of cocaine. This is consistent with our previous findings (6).

Hyperbaric conditions can reverse the effects of a wide variety of anesthetic agents in tadpoles (16). However, pressures of 70 ATA did not alter the metabolism of a wide range of drugs by isolated liver cells in vitro (8). It appears the authors used N_2-O_2 atmospheric conditions instead of He-O_2. This may account for their negative results, since we found that exposure of animals for 12 days to a 1.2-ATA He-O_2 (400 mmHg Po_2) environment caused significant elevation of drug-metabolizing enzyme activity as determined by the *O*-dealkylation of *p*-nitroanisole and the *N*-dealkylation of morphine. In support of this finding Alkana and Malcolm (17) found that 1 ATA He-O_2 antagonized the depressant action of alcohol over room-air control mice, and Tobey et al. (18) reported that thiopental sleeping times in guinea pigs were also shortened. It is interesting to note that hyperoxic conditions stimulated cytochrome P-450 formation in isolated hepatocytes (19). Cytochrome P-450 is one of the major constituents of the drug-metabolizing enzyme system.

Johnson et al. (20) first reported that hyperbaric conditions antagonize the effects of anesthetic agents. Since then other investigations have noted similar effects for diazepam (21), barbiturates (22–24), α-chloralose (25), ketamine (21), opiates (16, 26), tetrahydrocannabinol (27), amphetamine and chlordiazepoxide (23, 28), and alcohol (17, 29). However, neither Greenbaum and Evans (30) nor Curley et al. (31) reported changes in morphine analgesia for mice and rats exposed to 19.2 and 7.1 ATA He-O_2, respectively. It has also been reported that exposure of rats to a He-O_2 environment for 45 min did not affect the toxicity of pentobarbital, lidocaine, ethanol, or morphine (32).

Although some authors doubt that pharmacokinetic parameters are involved in pressure reversal of centrally active drugs (29), our results favor the importance of drug-metabolizing enzyme activation in reducing the effectiveness of drugs, not only under pressure but at 1.2 ATA He-O_2 (400 mmHg Po_2) as well. It seems clear that more work is needed to elucidate all the mechanisms involved.

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Geiger JD, Akers TK, Parmar SS. Effets des environnements d'hélium-oxygène sous pressions normales et élevées sur l'activité des enzymes responsables du métabolisme des drogues dans le foie du rat. Undersea Biomed Res 1983; 10(4):321–329.—Les effets de milieux ambients contenant de l'air normal (Po_2 de 150 mmHg, 22°C ± 1°C), He-O_2 à 1.2 ATA (Po_2 de 400 mmHg, 29.0°C ± 1°C) et He-O_2 à 21 ATA (Po_2 de 400 mmHg, 32.5°C ± 1°C) sur l'activité des systèmes enzymatiques responsables du métabolisme des drogues dans le foie du rat ont été investigués, tels que révélés par les réactions d'*O*-désalkylation et *N*-désalkylation. L'exposition continuelle des rats aux deux mélanges de He-O_2 pendant 12 jours augmenta significativement l'activité in vitro des enzymes responsables du métabolisme des drogues dans les préparations de foie. L'augmentation de la *O*-désalkylation de la *p*-nitroanisole in vitro, basée sur le produit formé/(mg protéine · 20 min), était de 32.2% ($P < 0.05$) entre les animaux en normoxie et ceux soumis à 1.2 ATA de He-O_2, et de 24.4% ($P < 0.01$) chez les rats exposés entre 1.2 et 21 ATA de He-O_2. Une élévation significative de 48.8% ($P < 0.01$) fut aussi trouvée entre les animaux en normoxie et ceux exposés à 21 ATA de He-O_2. Des différences similaires ont été notées lorsque les résultats furent exprimés sur la base de 200 mg de foie en poids mouillé. La *N*-désalkylation de la morphine, basée sur le produit formé/(mg de protéine · 20 min), était significativement augmentée de 17.6% ($P < 0.05$) chez les rats soumis aux conditions de normoxie et de 1.2 ATA de He-O_2, et de 28.8% ($P < 0.05$) chez les animaux gardés en milieux contenant de l'oxygène à la pression atmosphérique et de He-O_2 à 21 ATA. Aucune différence significative pour la *N*-désalkylation de la morphine n'a été observée chez les rats exposés à 1.2 et 21 ATA de He-O_2, ou chez tous les groupes d'animaux pour la *N*-désalkylation de la cocaine.

pression hyperbare
métabolisme des drogues
activité enzymatique
hélium
rat
morphine
cocaine

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