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TISSUE DISTRIBUTION OF IBOGAINE AFTER INTRAPERITONEAL AND SUBCUTANEOUS ADMINISTRATION

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Abstract. The distribution of the putative anti-addictive substance ibogaine was measured in plasma, brain, kidney, liver and fat after ip and sc administration in rats. One hr after ip dosing (40 mg/kg), drug levels ranged from 106 ng/ml (plasma) to 11,308 ng/g (fat), with significantly higher values after sc administration of the same dose. Drug levels were 10-20 fold lower 12 hr after the same dose. These results suggest that: 1) ibogaine is subject to a substantial "first pass" effect after ip dosing, demonstrated by higher drug levels following the sc route, 2) ibogaine shows a large accumulation in adipose tissue, consistent with its lipophilic nature, and 3) persistence of the drug in fat may contribute to a long duration of action.

Key Words: ibogaine, routes of administration, pharmacokinetics, addiction

Introduction

The indole alkaloid ibogaine is currently being investigated as a potential anti-addictive substance (U.S. patents 4,499,096 and 4,587,243; H. Lotsof). Despite the possibility that this compound may be capable of reducing or abolishing the self-administration of opiates (1), alcohol (2) and cocaine (3), very little information is available on the absorption, distribution, metabolism or excretion of this agent. An intriguing finding with ibogaine is its prolonged duration of action, with many effects on behavioral and neurochemical endpoints demonstrated one or more days later after administration (e.g. 1,4). Presently it is not known whether these prolonged effects are due to persistence of the drug in tissues, or due to other factors, such as an active metabolite (5). We recently described the development of a sensitive and specific analytical chemical method utilizing gas chromatography-mass spectrometry for measuring ibogaine in biological samples (6). Presently, we have applied this method and report preliminary studies on the distribution of ibogaine in tissues and plasma of rats.

Methods

Female Sprague-Dawley rats (250-300 g, Charles River, Kingston, NY), were housed individually

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under normal laboratory conditions with food and water ad lib. All animal procedures were approved by the Institutional Animal Care and Use Committee of the Albany Medical College. Ibogaine hydrochloride (Sigma Chemical Co., St. Louis, MO) was dissolved in distilled water at 10 mg/ml by sonication and gentle heating in warm water. Animals received ibogaine hydrochloride (40 mg/kg, 4 ml/kg, ip or sc) and were sacrificed 1 or 12 hr later by decapitation. Tissues were removed immediately and homogenized in 5 volumes of ice cold 0.4 N perchloric acid and the homogenate was centrifuged (20,000 g for 20 min). Subcutaneous fat was dissected from the dorsal upper body. Trunk blood was collected into a beaker previously rinsed with 500 USP units of heparin. The blood was transferred to a 10 ml Vacutainer tube (#6430, Becton Dickson and Co., Rutherford, NJ) containing 100 ml (143 USP units) of heparin and centrifuged (2,500 rpm for 10 min). The plasma was removed, acidified with an equal volume of 0.8 N perchloric acid, and mixed by hand shaking. Acidified plasma samples were kept on ice at least 30 min and then centrifuged (1,200 g for 5 min). One ml aliquots of supernatant fractions were mixed with internal standard (O-[Cd_3]-ibogaine, 250 ng, synthesized as previously described, 6) and assayed for ibogaine exactly as previously described (6). Briefly, the method consists of organic extraction, derivatization with trifluoroacetic anhydride, and detection by combined gas chromatography-mass spectrometry in selected ion mode. The method yielded a detection limit of approximately 5 ng/ml, with a coefficient of variation of 2 - 4 %. Standard curves were constructed by the addition of varying amounts of ibogaine (20 to 400 ng) and internal standard (250 ng) to plasma and tissue homogenates from untreated animals. The standard curves obtained from the analysis of blank perchloric acid, tissue homogenates or plasma were indistinguishable. Except for the dose of ibogaine administered to animals (which is specified as amounts of hydrochloride salt), all units of ibogaine are given as the free base. Data were analyzed by a 3-factor (tissue, route, time) analysis of variance (ANOVA) and Neuman-Keuls post-hoc comparisons.

Results

Ibogaine levels from plasma, brain, kidney, liver and fat are shown 1 and 12 hr after ip or sc administration (Fig. 1). ANOVA revealed highly significant ($P < 0.001$) differences in drug levels from different tissues, after different routes of administration and at different times. Two interaction terms were also significant in the ANOVA (tissue X time and injection X time, $P < 0.05$). One hr after ip administration, an exceptionally large accumulation of ibogaine in adipose tissue was evident. Drug levels in fat were 11,308 ng/g, over 100-fold greater than plasma levels (106 ng/g). Drug levels in the other tissues were intermediate. Brain levels were also significantly elevated (about 30-fold) as compared with plasma. In nearly all samples, ibogaine levels after sc dosing were substantially greater than comparable values after ip administration. Twelve hr after drug administration, plasma and tissue levels were 10-20 fold lower as compared with 1 hr. A significant accumulation of drug was still evident in fat after sc dosing, however.

Discussion

The present results demonstrate a widespread distribution of ibogaine throughout the body. Particularly noteworthy are the high concentrations of drug in brain and fat. The 100-fold concentration of drug in fat is consistent with the highly lipophilic nature of ibogaine (Zetler et al. (7) reported a heptane/water partition coefficient of 28 for ibogaine). Levels in brain were approximately 10-20 μM (ip-sc, respectively) at one hour and dropped to 0.2-0.8 μM at 12 hours. Levels in fat were 40-50 μM at one hour, but were still 2-5 μM 12 hours later. The affinities of ibogaine for kappa opioid (8) and NMDA (9) receptors, as well as for the serotonin transporter (5), are approximately 1-2 μM. Thus, while the acute effects (less than 12 hours) of ibogaine may be attributable to the actions of ibogaine itself in the brain, prolonged effects (one or more days) are

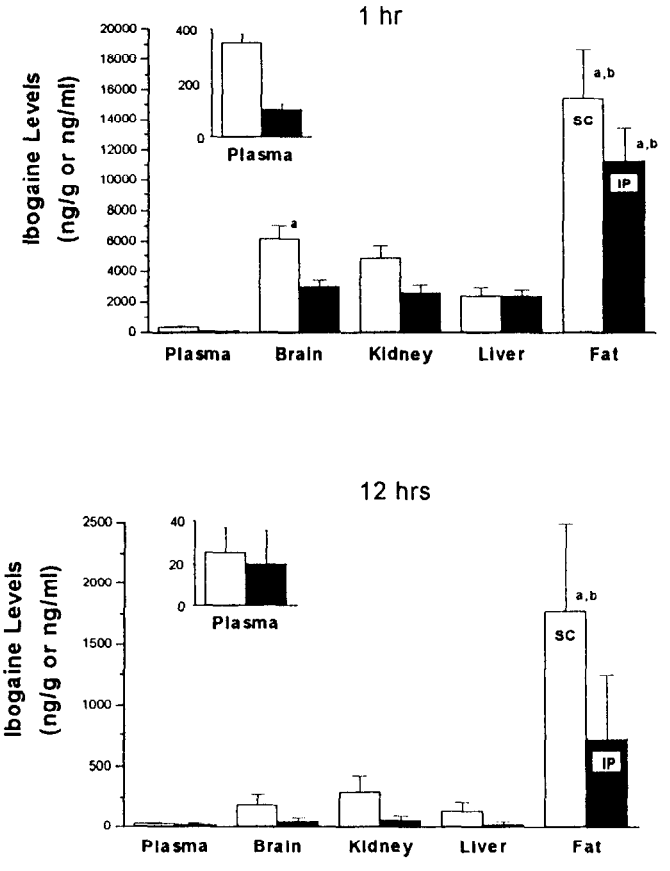

Fig. 1

Distribution of ibogaine in rat tissues. Animals received ibogaine (40 mg/kg), administered sc (open bars) or ip (solid bars) and were decapitated either 1 hr (top) or 12 hr (bottom) later. Ibogaine levels (ordinate, ng/g or ng/ml, mean ± S.E.M. n = 6-21), measured by gas chromatography-mass spectrometry, are shown for the tissues identified (abscissa). ANOVA showed that sc dosing yielded significantly higher drug levels when compared with ip dosing. [a]Significantly ($P < 0.01$) different from plasma values at the same time by the same route. [b]Significantly different from brain, kidney and liver values at the same time by the same route.

more likely to be attributable to a persisting metabolite (5). However, adipose tissue may serve as a reservoir of ibogaine, providing for its release and metabolism over a long time period.

The present study compared the sc and ip routes of administration in attempt to assess the possible significance of hepatic extraction after ip dosing. It was also of interest to compare these routes because of the suggestion that ibogaine metabolites (e.g., noribogaine) might account for some of the drug's activity (5). The present results show considerably higher drug levels in most tissues after sc administration, suggesting the importance of hepatic extraction of drug after ip dosing. This result is particularly interesting in view of a recent report that ip- and orally-administered ibogaine depresses alcohol self-administration whereas sc-administered ibogaine has no such effect (2).

Although the present results do not constitute a comprehensive pharmacokinetic analysis, they do suggest that a large proportion of the drug has been removed from the body within the first 12 hr after dosing. However, adipose tissue remains as a likely drug reservoir, and could account for low, sustained levels of drug in the body for long time periods. Consistent with this, ongoing pharmacokinetic studies of iv ibogaine suggest a multi-compartmental elimination model (unpublished observations).

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References

1. S.D. GLICK, K. ROSSMAN, S. STEINDORF, I.M. MAISONNEUVE AND J.N. CARLSON, Eur. J. Pharmacol. 195 341-345 (1991).
2. A.H. REZVANI, D.H. OVERSTREET AND Y. LEE, Pharmacol. Biochem. Behav. 52 615-620 (1995).
3. S.L.T. CAPPENDIJK AND M.R. DZOLJIC, Eur. J. Pharmacol. 241 261-265 (1993).
4. I.M. MAISONNEUVE, R.W. KELLER AND S.D. GLICK, Eur. J. Pharmacol. 199 35-42 (1991).
5. D.C. MASH, J.K. STALEY, M.H. BAUMANN, R.B. ROTHMAN AND W.L. HEARN, Life Sci. 57 PL45-50 (1995).
6. C.A. GALLAGHER, L.B. HOUGH, S.M. KEEFNER, A. SYED-MOZAFARRI, S. ARCHER AND S.D. GLICK, Biochem. Pharmacol. 49 73-79 (1995).
7. G. ZETLER, G. SINGBARTL AND L. SCHLOSSER, Pharmacology 7 237-248 (1972).
8. D.C. DEECHER, M. TEITLER, D.M. SODERLUND, W.G. BRONMANN, M.E. KUEHNE AND S.D. GLICK, Brain Res. 571 242-247 (1992).
9. P. POPIK, R.T. LAYER AND P. SKOLNICK, Pharmacol. Rev. 47 235-252 (1995).