

—CHAPTER 12—

## ANXIOGENIC ACTION OF IBOGAINE

PIOTR POPIK  
MALGORZATA WRÓBEL

*Institute of Pharmacology  
Polish Academy of Sciences  
31-343 Kraków, Poland*

I. Introduction.....	.....
II. Ibogaine and Anxiety.....	.....
A. Experimental Rationale.....	.....
B. Experimental Methodology.....	.....
C. Results.....	.....
III. Discussion.....	.....
References.....	.....

### I. Introduction

Almost 100 years ago, Dybowski and Landrin (1), as well as Haller and Heckel (2), isolated a crystalline alkaloid from the root of West African shrub, *Tabernanthe iboga* and named it “ibogaine.” Ibogaine was “rediscovered” during the past decade because of the anecdotal (3) and preliminary clinical (4,5) observations suggesting that it may offer a novel means of treating drug addictions. Preclinical studies are, in general, consistent with these claims. Thus, ibogaine reduces self-administration of cocaine (6) and morphine (7), attenuates the severity of morphine withdrawal (8,9), and inhibits conditioned place preference produced by morphine and amphetamine (10,11).

The neurochemical actions of ibogaine and related alkaloids were intensively investigated during the past decade, which has witnessed increasing growth of information attempting to explain the “antiaddictive” effects of ibogaine. The majority of work concentrated on its neurochemical effects, in the hope of identifying neuronal receptors and systems affected by this molecule. These findings, described in detail in the present and former volumes of *The Alkaloids*

(12-14), have profound implications for both understanding the mechanism of action of ibogaine and the molecular mechanism of drug addiction and dependence. Ibogaine affects a substantial number of neurotransmitter pathways, including *N*-methyl-D-aspartate (NMDA) and  $\kappa$ -opioid receptors, as well as dopamine and serotonin uptake sites and  $\sigma$  sites [for a review, see (14)]. However, the “antiaddictive” effects of ibogaine are still poorly understood, particularly at the psychological level.

In the current paradigm of drug development, findings gained in behavioral research ultimately direct our understanding of the drug’s mechanism of action, provide evidence of its effectiveness in an animal model, and ultimately decide whether a substance becomes a therapeutic agent (15). Findings gathered in behavioral studies often raise questions concerning whether the given substance may or may not be effectively used in a given clinical application, and also about its “side effects.” In addition, the effects found in behavioral studies that are not directly related to the purported mechanism of action often raise new questions such as the relevance of a “side effect” to a therapeutic action. This appears to be the case for ibogaine that, besides diminishing self-administration of drugs of abuse and alleviating the severity of opioid withdrawal, produces psychotomimetic effects, affects learning and memory processes (16-18), and has anxiogenic actions (14).

It is beyond the scope of this overview to provide direct evidence linking these “miscellaneous” or “side-effect”-like actions of ibogaine to its purported “antiaddictive” effects. Nonetheless, these “miscellaneous” or “side-effect”-like actions of ibogaine cannot be neglected, since they may indeed have some therapeutic implications, and their understanding may facilitate the discovery of its molecular mechanism(s) of action.

Operant and classical conditioning, habituation, and sensitization play important roles in determining the level of drug tolerance, addiction, dependence, and craving (19). Thus, inhibitory effects of ibogaine on drug addiction could be linked to a general interference with learning and memory processes. Often, drug-addicted individuals do not realize the roots of their habits—why they are, indeed, drug addicted. There are numerous possibilities, including traumatic experiences, such as events that took place in childhood. It can be hypothesized that a therapy, able to uncover these experiences, would be helpful in localizing and eliminating the cause of the disorder. This is the role of the psychotherapist, but perhaps with the help of ibogaine, this role could be made easier.

It is known that ibogaine produces a variety of psychotomimetic effects. It is debatable whether these are important from the clinical perspective. It would be hard to argue that the “antiaddictive” effects in laboratory animals are due to the hallucinogenic actions. It is also worth noting that there are many psychotomimetic compounds that are not “antiaddictive.” Nonetheless, Naranjo, who explored the possibility of using ibogaine to facilitate psychotherapy,

concluded that ibogaine could act as a psychological catalyst, which could compress a long psychotherapeutic process into a shorter time (20).

## II. Ibogaine and Anxiety

### A. EXPERIMENTAL RATIONALE

In humans, ibogaine has been reported to produce anxiety, fear, and apprehension (21). These effects are important, as they may influence the process of psychotherapy and/or in some cases, can be regarded as a confounding factor. Recently, Benwell and colleagues (22), while studying the possible effects of ibogaine on the neurochemical actions of nicotine in rats, found that ibogaine administered at the dose of 40 mg/kg, 22 hours before the test, produced an anxiogenic effect. It must be considered that such an anxiogenic effect of ibogaine may confound several measures of drug-seeking and taking behavior in animal models of drug addiction. The present work was designed to determine if the same effects on anxiety could be identified in mice following the administration of lower doses of ibogaine given after a shorter time interval.

### B. EXPERIMENTAL METHODOLOGY

#### 1. *Animals*

Male Albino Swiss mice (26-32 g) obtained from the Institute of Pharmacology breeding facility, were housed under standard laboratory conditions (lights on at 0600 hours, lights off at 1800 hours; room temperature  $23 \pm 1^\circ$ ) with pelleted food and tap water available *ad libitum*. They were kept in 43 x 27 x 15 cm plastic cages (eight mice per cage). All animals were used only once.

#### 2. *Drugs*

Hydrochloride salt of ibogaine (Sigma) and the reference compound picrotoxin were dissolved in the physiological saline that served as a placebo. Injections were done i.p. in the volume of 10 ml/kg. The selection of doses was based on previous studies with ibogaine (22) and picrotoxin (23,24).

#### 3. *Apparatus and Procedure*

An elevated plus maze (23) was used to study the anxiety in mice. It was made of plywood and consisted of two open arms (30 x 5 cm) and two enclosed arms (30 x 5 x 15 cm). The arms extended from a central 5 x 5 cm platform. The maze was painted black and mounted on a wooden base, raising it 50 cm above the

floor. The apparatus was lit with two 15-watt lightbulbs placed 60 cm above the open arms.

The experiments were carried out between 0900 and 1700 hours. Drugs were administered 30 minutes before the test that lasted for 5 minutes. Mice were tested in an order counterbalanced for the treatment condition. There were 8 to 10 mice in each group. Mice were placed on the central platform, and the time spent on each of the four arms as well as the number of entries into arms was manually recorded using PLUS MAZE 2.0 program on a PC-compatible computer. After each mouse, the apparatus was cleaned and dried. The experimenter was blind to the treatment condition. The percentage of open/total time ( $[\text{open arm time}/\text{open arm} + \text{closed arm time}] \times 100$ ) as well as the percentage of open/total arm entries ( $[\text{open arm entries}/\text{open arm} + \text{closed arm entries}] \times 100$ ) served as the measures of anxiety. The number of closed arm entries was used as the measure of locomotor activity.

The experiments were carried out according to the National Institutes of Health Guide for Care and Use of Laboratory Animals (publication No. 85-23, revised 1985) and were approved by the internal Bioethics Commission.

TABLE 1.  
ANXIOGENIC EFFECTS OF IBOGAININE IN MICE

Treatment (mg/kg)	% Open/total time	% Open/total arm entries	Closed arm entries [n]
Placebo [10]	6.21 ± 1.33	18.6 ± 1.36	13.1 ± 0.81
Ibogaine 10 [10]	3.07 ± 1.33	10.3 ± 3.12	12.3 ± 1.34
Ibogaine 20 [10]	2.03 ± 0.90*	10.7 ± 2.96	11.2 ± 0.73
Ibogaine 40 [9]	1.56 ± 0.73*	5.77 ± 2.50**	10.4 ± 1.27
ANOVA	F(3,35) = 3.49, P<0.05	F(3,35) = 4.21, P<0.05	F(3,35) = 1.19, NS
Placebo [10]	7.53 ± 0.86	20.8 ± 1.66	12.6 ± 0.68
PIC 0.25 [8]	5.03 ± 1.10	16.0 ± 1.85	12.0 ± 1.39
PIC 0.5 [8]	3.64 ± 1.19*	13.2 ± 2.66	11.4 ± 1.29
PIC 1 [10]	0.56 ± 0.35***	9.15 ± 3.83*	6.20 ± 0.83***
ANOVA	F(3,32) = 11.9, P<0.001	F(3,32) = 3.53, P<0.05	F(3,32) = 8.81, P<0.0001

Presented are means ± S.E.M. of: (1) percentage of open/total arm time, (2) percentage of open/total arm entries, and (3) the number of closed arm entries in the elevated plus maze. Results of (1) and (2) reflect the measures related to the anxiety. The number of closed arm entries is regarded as the measure of general locomotor activity. Mice were treated with placebo (physiological saline), ibogaine, and picrotoxin [PIC] 30 minutes before the test.

NS not significant

\* (P < 0.05)

\*\* (P < 0.01)

\*\*\* (P < 0.001)

Statistically significant difference compared to placebo treatment (Newman-Keul's Multiple Comparison Test). The number of mice used for each dose is indicated in the brackets.

#### 4. *Statistical Analysis*

For the statistics, one way between subjects ANOVA was performed for each treatment condition, followed by Newman-Keul's multiple comparison post-hoc test.

### C. RESULTS

Ibogaine reduced the percentage of open/total arm time (20 and 40 mg/kg) and the percentage of open/total arm entries (40 mg/kg). The decrease of the percentage of open/total time and the percentage of open/total arm entries produced by ibogaine was comparable to that observed in mice treated with picrotoxin (0.5 and 1 mg/kg) (Table I). Mean locomotor activity (closed arm entries) was not affected by the drugs tested, with the exception of picrotoxin (1.0 mg/kg) (Table I).

### III. Discussion

The elevated plus maze (25) offers a reliable means of investigating anxiety in rodents. Ibogaine and picrotoxin reduced the percentage of open/total time as well as percentage of open/total arm entries, indicating that these compounds increased the anxiety. The anxiogenic effect of picrotoxin is well known (23,25) and therefore supports the use of this compound as reference. As in our study, Dalvi and Rodgers (24) reported that the anxiogenic effect of picrotoxin in mice at doses higher than or equal to 1 mg/kg was confounded by the behavioral suppression.

Perhaps the first documented notion that ibogaine produces a subjective state of anxiety was made by Sigg, who, after ingestion of 200 mg of ibogaine, reported: "Subjectively, the most unpleasant symptoms were the anxiety, the extreme apprehension, and the unheimliche Grundstimmung (~unfamiliar mood) associated with visual and bodily hallucinations" (26), p. 94. More recent studies indicate that ibogaine reduced the number of open arm entries in the elevated plus-maze test in rats tested 22 hours after pretreatment with ibogaine (40 mg/kg, i.p.). Such a long time between the drug administration and the test may suggest the involvement of a long-lasting ibogaine metabolite, since ibogaine's plasma half-time in rodents is about 1 hour (27).

Ibogaine affects a substantial number of neurotransmitter pathways, including NMDA and  $\kappa$ -opioid receptors, as well as dopamine and serotonin uptake sites and  $\sigma$  sites [for a review, see (14)]. Ibogaine antagonistic activity at NMDA receptors cannot explain its anxiogenic effects, because NMDA receptor

antagonists reduce, rather than increase, anxiety in rodents (28). The high affinity of ibogaine at the  $\kappa$ -opioid receptors is supported by its ability to block the effects of a  $\kappa$ -opioid agonist to inhibit dopamine and serotonin release (29), suggesting that ibogaine may act as a  $\kappa$ -opioid antagonist. This is, in turn, supported by findings indicating that  $\kappa$ -opioid agonists produce anxiolytic effects in the elevated plus maze in rats (30). However, in light of other reports suggesting agonist activity of ibogaine at  $\kappa$ -opioid receptors (31), it remains to be assessed whether ibogaine's activity at  $\kappa$ -opioid receptors plays a role in its anxiogenic effect.

In conclusion, it remains to be established whether the acute (present study) and delayed (22) anxiogenic effects of ibogaine are related to its inhibitory effects on drug-seeking and taking behavior or if it may be regarded only as the confounding factor. Alternatively, it is possible that the anxiogenic actions of ibogaine revealed in mice may have nothing to do with their putative antiaddictive actions in humans.

### Acknowledgments

This work was supported by the statutory activity of the Institute of Pharmacology Polish Academy of Sciences.

### References

1. J. Dybowski and E. Landrin, *C. R. Acad. Sci. (Paris)* **133**, 748 (1901).
2. A. Haller and E. Heckel, *Compt. Rend. Soc. Biol.* **133**, 850 (1901).
3. H.S. Lotsof, *U.S. Patent* 4,499,096 (1985).
4. S.G. Sheppard, *J. Subst. Abuse Treat.* **11**, 379 (1994).
5. K.R. Alper, H.S. Lotsof, G.M.N. Frenken, D. Luciano, and J. Bastiaans, *Am. J. Addict.* **8**, 234 (1999).
6. S.L.T. Cappendijk and M.R. Dzoljic, *Eur. J. Pharmacol.* **241**, 261 (1993).
7. S.D. Glick, M.E. Kuehne, J. Raucci, T.E. Wilson, D. Larson, R.W. Keller, and J.N. Carlson, *Brain Res.* **657**, 14 (1994).
8. P. Popik, R.T. Layer, L. Fossom, M. Benveniste, B. Getter-Douglas, J.M. Witkin, and P. Skolnick, *J. Pharmacol. Exp. Ther.* **275**, 753 (1995).
9. R.T. Layer, P. Skolnick, C.M. Bertha, M.E. Kuehne, and P. Popik, *Eur. J. Pharmacol.* **309**, 159 (1996).
10. I. Moroz, L.A. Parker, and S. Siegel, *Exp. Clin. Psychopharm.* **5**, 119 (1997).
11. L.A. Parker, S. Siegel, and T. Luxton, *Exp. Clin. Psychopharm.* **3**, 344 (1995).
12. W.I. Taylor, in "The Alkaloids: Chemistry and Physiology" (R.H.F. Manske, ed.), Volume 8, p. 203. Academic Press, New York, NY, 1965.

13. W.I. Taylor, in "The Alkaloids: Chemistry and Physiology" (R.H.F. Manske, ed.), Volume 11, p. 79. Academic Press, New York, NY, 1968.
14. P. Popik and P. Skolnick, in "The Alkaloids: Chemistry and Biology" (G.A. Cordell, ed.), Volume 52, p. 197. Academic Press, San Diego, CA, 1999.
15. P. Willner in "Behavioural Models in Psychopharmacology: Theoretical, Industrial and Clinical Perspectives" (P. Willner, ed.), p. 3. Cambridge University Press, Cambridge, 1991.
16. R.P. Kesner, P. Jackson-Smith, C. Henry, and K. Amann, *Pharmacol. Biochem. Behav.* **51**, 103 (1995).
17. P. Popik, *Life Sci.* **59**, 379 (1996).
18. S. Helsley, D. Fiorella, R.A.Rabin, and J.C.Winter, *Pharmacol. Biochem. Behav.* **58**, 37 (1997).
19. S. Siegel, in "Psychopathology in Animals, Research and Clinical Implications" (J.D. Keehn, ed.), p. 143. Academic Press, New York, NY, 1979.
20. C. Naranjo, *Clin. Toxicol.* **2**, 209 (1969).
21. J.A. Schneider and E.B. Sigg, *Ann. N.Y. Acad. Sci.* **66**, 765 (1957).
22. M.E.M. Benwell, P.E. Holtom, R.J. Moran, and D.J.K. Balfour, *Br. J. Pharmacol.* **117**, 743 (1996).
23. R.G. Lister, *Psychopharmacology* **92**, 180 (1987).
24. A. Dalvi and R.J.Rodgers, *Psychopharmacology* **128**, 380 (1996).
25. S. Pellow, P. Chopin, S.E. File, and M. Briley, *J. Neurosci. Meth.* **14**, 149 (1985).
26. J.A. Schneider and E.B. Sigg, in "Progress in Neurobiology. Psychopharmacology; Pharmacologic Effects on Behavior" (H.H. Pennes, ed.), p. 75. New York, NY, 1958.
27. H.I. Dhahir, *Diss. Abstr. Int.* **32/04-B**, 2311 (1971).
28. J.L. Wiley, A.F. Cristello, and R.L. Balster, *Eur. J. Pharmacol.* **294**, 101 (1995).
29. H. Sershen, A. Hashim, and A. Lajtha, *Brain Res. Bull.* **36**, 587 (1995).
30. T.H. Privette and D.M. Terrian, *Psychopharmacology* **118**, 444 (1995).
31. S.D. Glick, I.M. Maisonneuve, and S.M. Pearl, *Brain Res.* **749**, 340 (1997).

