——Chapter 10——

# IBOGAINE NEUROTOXICITY ASSESSMENT: ELECTROPHYSIOLOGICAL, NEUROCHEMICAL, AND NEUROHISTOLOGICAL METHODS

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## I. Introduction

Ibogaine, a psychoactive indole alkaloid, is derived from the root bark of the tropical shrub *Tabernanthe iboga*. The powdered root bark of *T. iboga* is used for medicinal and religious purposes in the Bwiti cult in Gabon (*1*). Anecdotal reports and published studies in laboratory animals have indicated that ibogaine may reduce the craving for cocaine (*2*,*3*). Ibogaine is also reportedly effective in the blockade of morphine self-administration and decreasing the signs of opiate withdrawal (*4*). Worldwide social and medical problems of substance abuse make evaluating the efficacy of potential compounds exhibiting antiaddictive properties of prime importance. However, in animal studies, ibogaine administration has been associated with neurotoxic side effects. Observations from several labora-

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tories, including our own, of ibogaine's neuronal cytotoxicity in rats, have raised the question of whether treatment of substance dependence with ibogaine may also lead to ibogaine-induced neurotoxicity (*5-7*)

Interactions have been reported between ibogaine and many neurotransmitter systems, (i.e., dopaminergic, serotonergic, opioid, glutamate, nicotine, noradrenergic, and cholinergic, reviewed by Popik and Skolnick [*8*]). Thus far, it is not completely understood how those interactions contribute to ibogaine's putative antiaddictive effects. The involvement of the dopaminergic system is described in publications from multiple laboratories (*9-11*). Acute *in vivo* response to ibogaine has been reported to involve a decrease in striatal and cortical dopamine concomitant with an increase in dopamine metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and dopamine turnover (*11*). Increased or decreased dopamine levels in specific brain regions have been seen, together with increased or decreased motor activity after amphetamine or cocaine administration and ibogaine pretreatment (*12,13*).

A complex ibogaine interaction with other neurotransmitter receptor sites has been suggested to have modulatory effects on the dopamine system. For example, it has been speculated that ibogaine's action as an NMDA antagonist (*14*), together with kappa-opioid agonist and nicotinic antagonist effects, underlies the ibogaine modulatory effect (*15*). Other complex interactions have also been proposed to explain the mechanisms of ibogaine's therapeutic actions. Recently, neurotensin, a neuromodulator peptide, has been suggested to be an important intermediary in ibogaine's apparent antiaddictive actions against cocaine's stimulation of the dopaminergic system (*16*).

The chemical structure of ibogaine is similar to serotonin (5-HT) and melatonin. Several *in vitro* and *in vivo* studies indicated that the serotonergic system plays a role in ibogaine actions (*10,13,19*). In fact, acute behavioral responses (tremor, ataxia) in rats to ibogaine, particularly at high doses (*17*), resemble a stereotyped behavioral response observed after central serotonergic stimulation (*18*). Ibogaine was also reported to increase extracellular 5-HT concentration in rat striatum and nucleus accumbens (*19,20*). The 5-HT-like response to ibogaine may result from a direct action of ibogaine on 5-HT receptors and/or ibogaine-induced increase in 5-HT level.

## II. Electroencephalography and Ibogaine

Electroencephalography (EEG) is a technique applied in the assessment of spontaneous electrocerebral activity using either scalp (surface) electrodes, or in the case of the electrocorticogram (ECoG), from electrodes implanted in specific

brain regions. Electrocerebral activity represents local action potentials and widespread excitatory and inhibitory postsynaptic potentials. The ECoG records an average of synchronous, widespread postsynaptic potentials arising in vertically oriented pyramidal cells of the upper layers of the cerebral cortex (*21*). EEG synchrony is reduced (desynchronization) by arousal and cognitive activity. On the other hand, reduced vigilance (drowsiness, sleep) increases synchrony. Transitory hypersynchronous cortical activity may also be elicited by afferent stimuli (evoked potentials), and pathological epileptiform discharges.

Rapid advances in computer technology during the past 20 years have allowed expansion of quantitative EEG analysis in neuroscience, as well as clinical neurology. Among the variety of techniques in this field, frequency (spectral) analysis provides a sensitive tool for time-course studies of different compounds acting on particular neurotransmitter systems. Frequency data are often analyzed as the power spectrum, measured as total power in microvolts-squared divided by frequency or over a particular power band.

The complex nature of ibogaine actions on neurotransmitters and neuromodulators in the cerebral cortex may have both an inhibitory and stimulatory effect on the neuronal firing reflected as the bioelectric neuronal activity and recorded as the EEG (*22*). We previously applied electroencephalography and spectral analysis to characterize the ECoG profiles in rats anesthetized with isoflurane and exposed to ibogaine or to one of two other NMDA receptor antagonists, MK-801 or phencyclidine (PCP). While some features of the neurochemical response to all three compounds were similar, a distinctly different EEG response to each treatment was observed (*23*). Recently, to extend our research on ibogaine neurotoxicity assessment, we aimed to analyze the effects of ibogaine/cocaine interaction on electrocerebral activity in conscious rats (*24*).

## A. EEG Study

Three-month-old, male, Sprague-Dawley rats of the Charles River cesarean delivered (CD) strain were used in this study. Bipolar stainless steel electrodes were implanted above the somatosensory cortex, 3 mm laterally from the sagittal fissure, 1 and 4 mm posterior to the bregma. They were referenced to a ground electrode placed in the dorsal neck. The ECoG was recorded via a tether and swivel system at least one week after implantation. During recording, the animals remained in a microdialysis bowl placed inside a Faraday cage. Amplified signals were rectified to pass frequencies of 1-40 Hz and processed with LabView software (National Instruments, Austin, Texas). The power spectra obtained by use of Fast Fourier Transformations were divided into 1.25-4.50 Hz (delta), 4.75-6.75 Hz (theta), 7.00-9.50 Hz ($alpha_1$), 9.75-12.50 Hz ($alpha_2$), 12.75-18.50 Hz ($beta_1$), and 18.75-35.00 Hz ($beta_2$) frequency bands. Following the recording of the 30-minute baseline ECoG in the morning, rats were either injected intraperi-

toneally (i.p.) with cocaine alone (20 mg/kg.) or pretreated i.p. with ibogaine (50 mg/kg), followed an hour later by cocaine (20 mg/kg).

## B. Results and Comments

Administration of cocaine was accompanied within 10 to 15 minutes after the injection by increased stereotypical behavior (hyperactive sniffing, chewing) and locomotor stimulation that lasted throughout the 60 minute recording. On the other hand, treatment with ibogaine alone produced tremors and ataxia. Administration of cocaine following ibogaine led to locomotor activity, but less than that observed after only cocaine.

Analysis of the ECoG in rats injected with ibogaine revealed a significant increase in total power (1-40 Hz) during first 30 minutes postinjection (Figure 1). A power increase in the theta frequency band lasting for approximately 10 minutes was observed. The total power was again significantly activated throughout the 60 minute recording when cocaine was injected after ibogaine pretreatment (Figure 1). Administration of cocaine alone was associated only with a significant power increase in the alpha1 frequency band during the first 30 min. postinjection (Figure 2). However, when cocaine was injected after ibogaine pretreatment, the alpha1 increase was maintained throughout recording. In addition, ibogaine/cocaine treatment resulted in a significant power increase in the delta and theta bands (Figure 3).

Studies have indicated that the alteration of ECoG patterns observed after cocaine administration appear to be related to increased release of dopamine in the striatum and prefrontal cortex (*25,26*). However, besides the dopaminergic effect of cocaine, (i.e., inhibition of dopamine reuptake), serotonergic effects of cocaine administration have also been reported (reviewed by Sershen *et al.* [*10*]). Ibogaine administered intraperitoneally is reported to markedly increase extracellular 5-HT in the nucleus accumbens and striatum (*19,20*). Activation of 5-HT receptors has been shown to the increase power in the $alpha_1$ band (*27*). The spectral patterns obtained after ibogaine/cocaine treatment in our study, mainly showing increased power in the low frequency bands and enhancement of power in the $alpha_1$ band, appear to indicate the contribution of the serotonergic system in the ibogaine-mediated response to cocaine.

Although no behavioral convulsive effects of cocaine injected after ibogaine were found, the enhancement of power observed in low frequency bands after the ibogaine/cocaine treatment may suggest that ibogaine at high dose decreases the threshold for cocaine-induced seizures. This effect seems to be contradictory to the fact that ibogaine was shown to be a neuroprotectant due to its NMDA noncompetitive antagonist action, suggesting that ibogaine should suppress seizures. However, a similar effect exerted by two other NMDA noncompetitive antagonists was reported earlier by other investigators. Ketamine and MK-801,

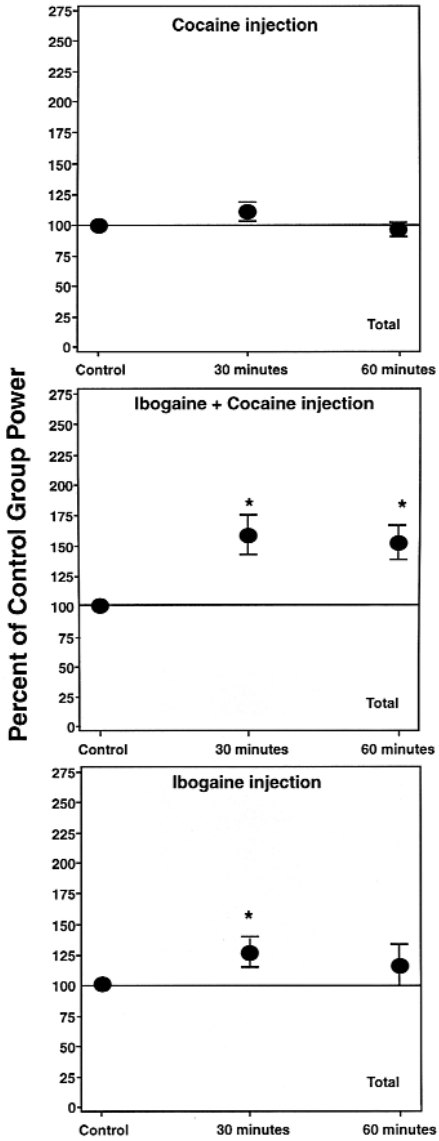


FIGURE 1. EFFECTS PRODUCED BY COCAINE (20 MG/KG), IBOGAINE (50 MG/KG) I.P., AND IBOGAINE PRETREATMENT 1 HR PRIOR TO COCAINE ON ELECTROENCEPHALOGRAPHIC ACTIVITY. Total = total power 1-40 Hz. Power values calculated as percent of the 30 min baseline power recorded after saline injection (assigned as a value of 100%). Mean ± SEM; n=3 rats
*$p<0.05$ significantly different from baseline.

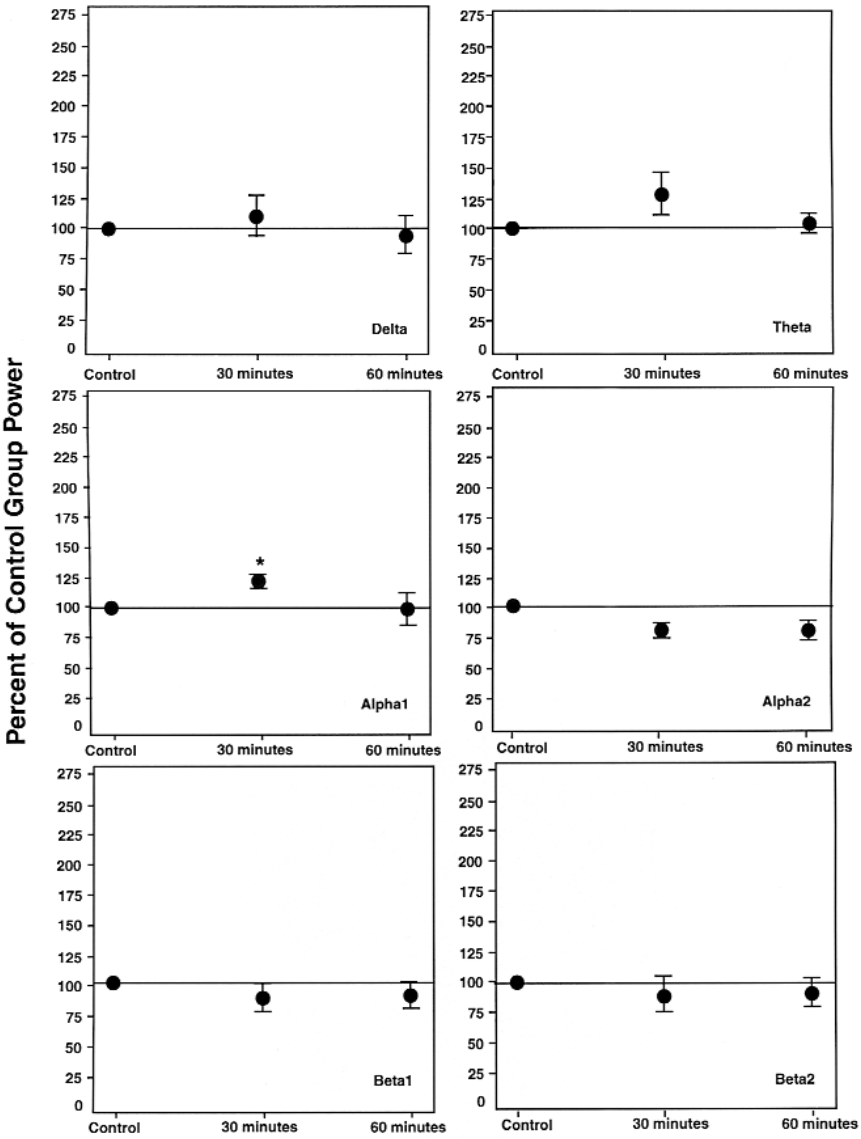


FIGURE 2. EFFECTS PRODUCED BY COCAINE ON THE CORTICAL POWER SPECTRA. Cocaine was injected at 20 mg/kg i.p. Power values calculated as percent of the 30 min baseline power recorded after saline injection (assigned as a value of 100% in each band). Mean ± SEM; n=3 rats.
*$p < 0.05$ significantly different from baseline.

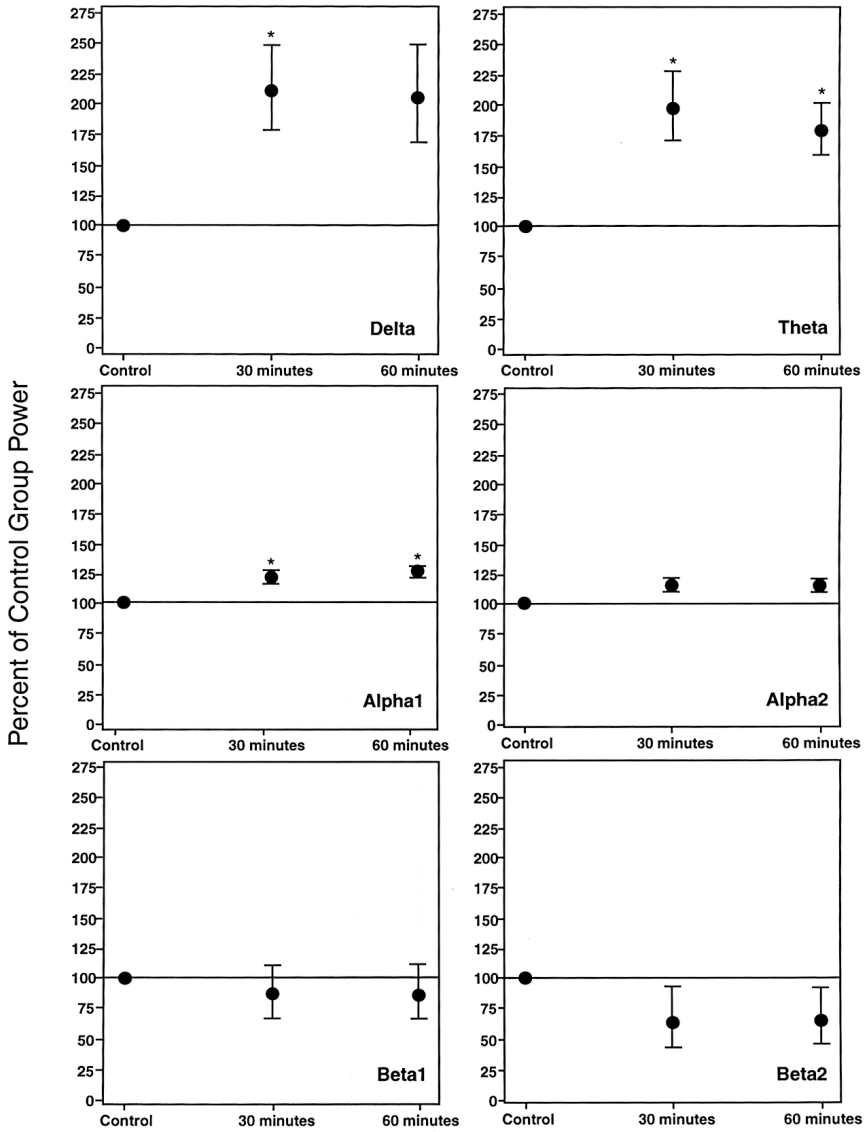


FIGURE 3. EFFECTS PRODUCED BY COCAINE INJECTED AT 20 MG/KG I.P. AND IBOGAINE PRETREATMENT AT 50 MG/KG I.P. 1 HR PRIOR TO COCAINE. Power values calculated as percent of the 30 min baseline power recorded after saline injection (assigned as a value of 100% in each band). Mean ± SEM; n=3 rats. *p<0.05 significantly different from baseline.

tested for their antiepileptic activity, induced a paradoxical enhancement of electrographic seizures that preceded suppression of status epilepticus (*28*). IBO, like MK-801, stimulates corticosterone release (*29*) and corticosterone has been shown to increase susceptibility to seizures (*30*).

## III. Other Studies on Ibogaine Neurotoxicity at FDA/NCTR

### A. Neurochemistry

Although ibogaine has been known to produce effects on multiple neurotransmitter systems, the neurochemical basis of ibogaine's effects is still poorly understood. Several reports have suggested that acute administration of ibogaine alters the extracellular concentration of dopamine and its metabolites in different regions of the rat and mouse brain (9,12). However, we have reported that pretreatment with ibogaine failed to alter either the spontaneous activity of ventral tegmental dopamine neurons or the response of these dopamine neurons to morphine or cocaine (31). The excitatory effects of ibogaine on ventral tegmental dopamine neurons are not long lasting, nor does ibogaine persistently alter cocaine- or morphine-induced changes in dopamine neuronal impulse activity.

In our collaborative time course study reported earlier (*11*), adult, male, CD strain Sprague-Dawley rats were treated with a single injection of ibogaine (50 mg/kg, i.p.). They were sacrificed at 15, 30, 60, 120 minutes, and 24 hours later by decapitation. Trunk blood was collected and brains were dissected into different regions. We have shown that acute injection of ibogaine produced a significant increase in blood plasma prolactin levels within 15 and 30 minutes. While prolactin was observed to return to the control level by 120 minutes (Figure 4a), the corticosterone concentration that increased within 15 minutes returned to the control level by 24 hours after ibogaine treatment (Figure 4b). Besides neuroendocrine alterations, ibogaine produced significant changes in monoamine neurotransmitter systems. A single injection of ibogaine produced a significant reduction in the dopamine concentration in the striatum after 30, 60, and 120 minutes. Dopamine levels returned to control values after 24 hours. The dopamine metabolites (DOPAC and HVA) increased significantly within 15 minutes after ibogaine administration and remained elevated up to 120 minutes. While HVA returned to the control level, DOPAC concentration decreased to below control values 24 hours after ibogaine administration. In the frontal cortex, the concentration of dopamine decreased 30 minutes after ibogaine injection and

returned to control values within 60 minutes (Figures 5a and b).

The endocrine profile observed in our ibogaine study resembles those obtained with the administration of other 5-HT releasing agents, such as fenfluramine (*32*). Our data suggest that ibogaine effects, like fenfluramine, might be mediated via stimulation of the serotonergic system. Ibogaine administration elicits a serotonergic-like syndrome, such as tremors and forepaw treading, and interactions between ibogaine and serotonergic system have been reported (*11,13*). In addition, the affinity of ibogaine for the 5-HT transporter is higher than for the dopamine transporter (*10*). Ibogaine produced time-dependent changes in the dopamine system, which also have been reported by several laboratories, including ours (*9-12,15*). However, these effects do not involve ibogaine binding to dopamine receptors (*13,19*). Ibogaine displays different dopamine transporter

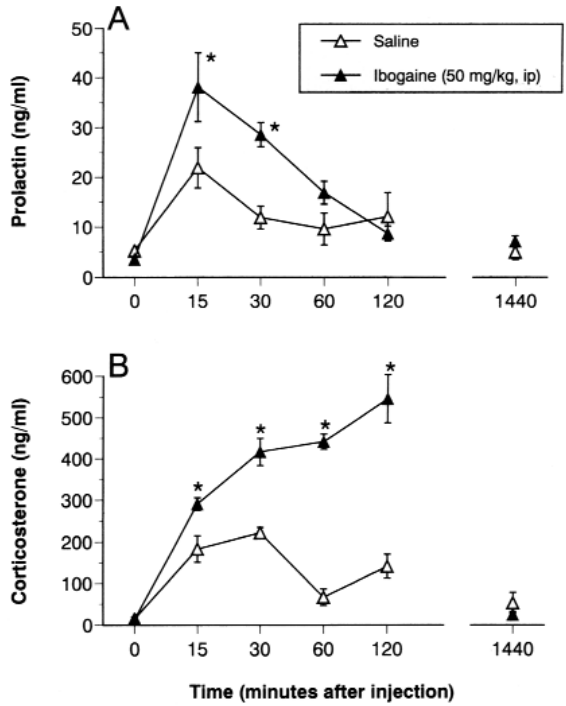


FIG. 4. EFFECTS OF SALINE (1 ML/KG, I.P.) OR IBOGAINE (50 MG/KG, I.P.) ON PLASMA PROLACTIN (A) AND CORTICOSTERONE (B) IN ADULT MALE RATS. Trunk blood was collected immediately before and at 15, 30, 60, 120 and 1440 minutes (24 h) after ibogaine administration. Data represent mean ± S.E.M. of n=4-8 rats/group.
*p<0.05 compared to saline treated group (Adopted from Ali *et al.*[*11*]).

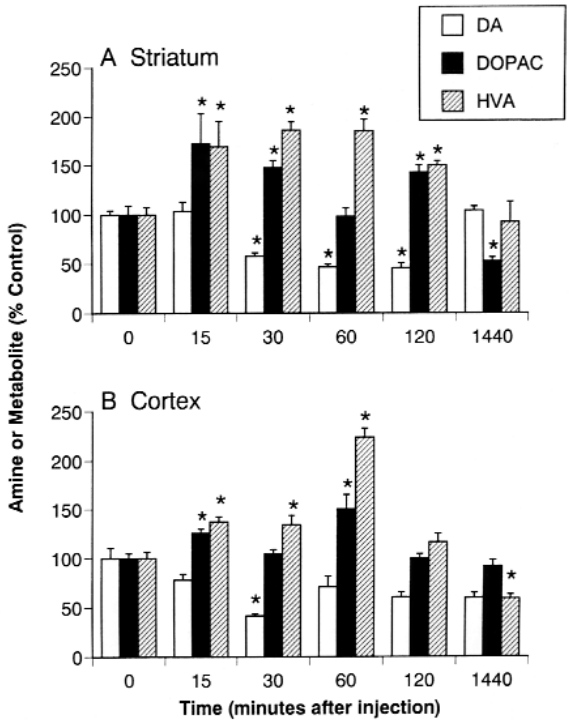


FIG. 5. EFFECTS OF IBOGAINE (50 MG/KG, I.P.) ON DA, DOPAC AND HVA CONCENTRATION IN THE STRIATUM (A) AND FRONTAL CORTEX (B) OF ADULT MALE RATS. Rats were sacrificed (n=4-8 rats/group) immediately before and at 15, 30, 60, 120 and 1440 min (24 hr) after ibogaine administration. Values are expressed as % of control of the data pooled from saline-treated rats at all time points (n=20).
*p<0.05 with respect to time zero control (Adopted from Ali *et al.*[*11*]).

binding affinity depending on the radioligand used to label these sites. Therefore, different domains may be present on the dopamine transporter protein that binds to ibogaine.

The neurochemistry/neurobiology of ibogaine is complex, and the binding of ibogaine to the multiple target sites in the central nervous system, and the coactivation of multiple transmitter systems, probably accounts for the diverse actions of this alkaloid, including its putatively antiaddictive effects.

## B. NEUROHISTOLOGY

In addition to a structural resemblance to 5-HT, ibogaine is closely related

structurally to harmaline, a tremorigenic agent known to produce neurotoxic damage to the cerebellum. This observation led O'Hearn and Molliver (*17*) to evaluate the neurohistology of the rat cerebellum following acute exposure to 100 mg/kg ibogaine, i.p. As with harmaline, they observed a loss of Purkinje neurons in the cerebellar vermis, as indicated by several neurohistological biomarkers: argyrophilic degeneration, loss of calbindin immunoreactivity, astrocytosis, and microgliosis. Efforts by other laboratories failed to obtain any evidence for the neurotoxicity of ibogaine in nonhuman primates (*33*). However, the methods used in those studies were primarily conventional hematoxylin and eosin (H and E) staining of paraffin sections, rather than the more specialized techniques of O'Hearn and Molliver.

Both the nature and the extent of ibogaine neurotoxicity, as well as its efficacy, must be understood in order that the risks and benefits can be appropriately balanced to provide the necessary information for regulatory decisions regarding the therapeutic use of ibogaine in humans. Therefore, our research group at FDA/NCTR replicated the initial observations of O'Hearn and Molliver (*6,17*), using their specialized neurohistological methods, which included degeneration-selective silver-staining of dead (argyrophilic) neurons, as well as several immunohistochemical approaches. We sought to eliminate, as much as possible, the controversy that had been generated during the early 1990s regarding their initial observations of ibogaine neurotoxicity. Just as O'Hearn and Molliver had reported, we also observed that a single i.p. dose of 100 mg/kg ibogaine produced "patches" of dead cerebellar Purkinje neurons (*6*). These "patches" comprised clusters of perhaps five to eight adjacent, or nearly adjacent, neurons that had died and become argyrophilic within a week after the ibogaine injection (*6*). Similar sized "patches" were observed by using antisera to reveal the enhanced presence of glial fibrillary acidic protein (GFAP; an astrocyte-specific protein) (*6,17*). As a third method to identify neuropathology, we highlighted the appearance of normal cerebellar Purkinje neurons by immunostaining the dense deposits of calbindin contained in each cell body. IBO treatment (100 mg/kg) resulted in similar "patches," each again about five to eight neurons long, where no calbindin-immunoreactive neurons could be observed (*6,17*). Our data thus strongly supported the initial report of ibogaine neurotoxicity (*17*), using essentially the same treatment and evaluation approaches (*6*). A third independent evaluation by Molinari *et al*. (*7*), using degeneration-selective silver-staining, has also confirmed the occurrence and character of ibogaine neurotoxicity in the rat cerebellum following 100 mg/kg, i.p., but not after a lower dose of 40 mg/kg, i.p.

Finally, our own recent dose-response study once again replicated the several previous observations of ibogaine neurotoxicity one week following doses of 100 mg/kg i.p. and additionally evaluated doses of 75, 50, and 25 mg/kg in female rats. This investigation also demonstrated the dose-response relationship, for each of the three different neuropathological techniques, by which ibogaine produced

signs of Purkinje cell damage. A dose of 25 mg/kg was the highest level at which no observable adverse effects (NOAEL) of ibogaine occurred in any of the rats evaluated by any of the techniques in our study. The most sensitive procedures seemed to be immunohistochemistry for GFAP in the cerebellar cortex and the silver stain for degenerating axons in the deep cerebellar nuclei. Both of these methods detected the effects of 50 mg/kg ibogaine in the same two rats (out of a total of six) that were tested at this dose. Clearly neurotoxic effects of ibogaine were apparent in all six rats dosed with either 75 mg/kg or 100 mg/kg of ibogaine. However, the degenerating "patches" of Purkinje neurons were narrower, and fewer of their degenerating axons (as projections terminating in the deep cerebellar nuclei) could be observed in the 75 mg/kg compared to 100 mg/kg rats (*34*).

As mentioned previously, ibogaine shows a close structural resemblance to melatonin and 5-HT, whose receptors are widely distributed in the cerebellum, and throughout the entire brain. We were interested in exploring other histological biomarkers, such as c-fos, to comprehensively demonstrate the localization of brain cells activated by ibogaine (*35*,*39*). These data on regional c-fos responses may be compared to the effects of ibogaine on EEG described above. Previously, localization of c-fos activation has been compared to EEG findings for the convulsant neurotoxicants such as kainic acid and domoic acid (*36*,*37*). Under control conditions, only scattered and occasional neuronal nuclei express immunoreactive c-fos, an early-immediate gene product, located throughout the brain. However, stimuli resulting in the generation of neuronal action potentials have been shown to effectively initiate c-fos expression (*38*). Indeed, in our studies, exposure to 100 mg/kg of IBO evoked a widespread pattern of c-fos expression that served to indicate the specific regions of the brain that were most affected by ibogaine (*39*).

We believed that mapping the locations of c-fos activation might afford further insight into both the therapeutic and neurotoxic actions of ibogaine, so that the two might be dissociated. Intact excitatory input to the Purkinje neurons is required for the neurotoxic action of either harmaline or ibogaine (*17*). This may be demonstrated by using systemic injections of the neurotoxicant 3-aminopyridine to lesion the inferior olive, which provides the climbing fibers that ascend from the brainstem and innervate the Purkinje neurons. Under these circumstances, neither harmaline nor ibogaine can effectively produce cerebellar neurotoxicity (*17*). It was interesting to note that c-fos in the nuclei of the inferior olivary neurons was greatly increased following ibogaine exposure (*39*, and see Figure 6). Patches of cerebellar Purkinje neurons and their nearby granule cells also were strongly stimulated to express c-fos (*39*). Thus, it is likely that ibogaine's excitation of this pathway, which contains endogenous glutamate and/or aspartate, each capable of causing "excitotoxic" neurotoxicity, is sufficient to explain the loss of Purkinje neurons that was observed.

However, many other regions of the rat brain, where no neurotoxicity can be observed, are also induced into increased c-fos expression by ibogaine (*39*, and see Figures 6 and 7). These especially include neurons located throughout the rat neocortex, as well as the granule cells of the dorsal blade of the hippocampal dentate gyrus, and the pyramidal neurons of the hippocampal CA1 region. Ibogaine's strong activation of c-fos in the hippocampus may well relate to its induction of the EEG theta rhythm, as we previously observed (*24*), since theta rhythms are thought to arise from the hippocampal CA1 region in rats (*40*).

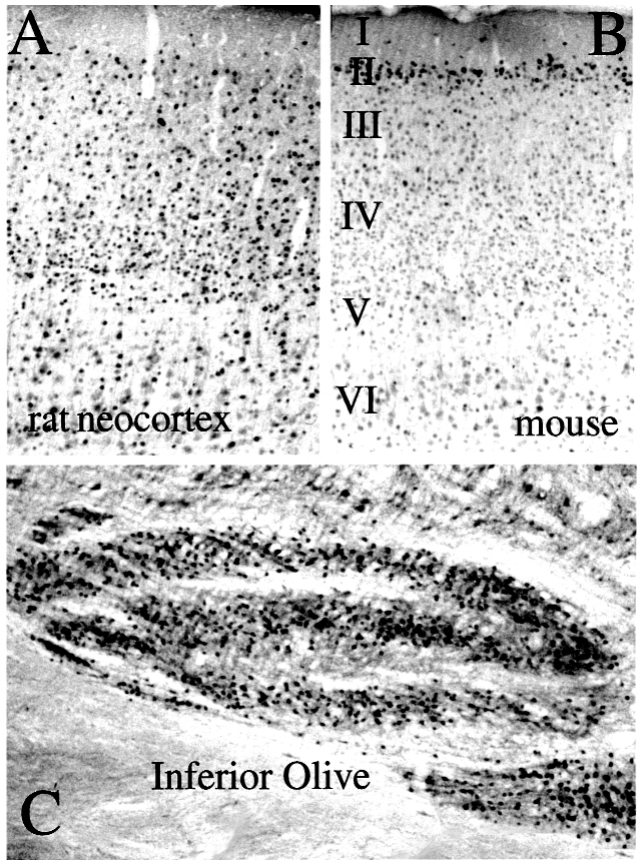


FIG. 6. A. and B. Ibogaine-induced c-fos restricted mainly to layer II of the mouse cortex, but, in the rat, considerable c-fos activation occurs throughout the deeper cortical layers, as well. C. Ibogaine induces many c-fos-immunoreactive neuronal nuclei in the inferior olive. These neurons project excitatory climbing fibers to innervate the Purkinje neurons of the cerebellum.

The paraventricular nucleus (PVN) of the hypothalamus is also highly activated by ibogaine (*39*, and see Figure 7b). The PVN is an important neurosecretory nucleus and regulator of the pituitary. Since its parvocellular neurons contain nearly all of the hypothalamic neuropeptide corticotrophin-releasing hormone (CRH), the effects of ibogaine on neuroendocrine functions, such as corticosterone release, may thus be explained. These additional effects of ibogaine outside the cerebellum may also be relevant to its psychoactive and

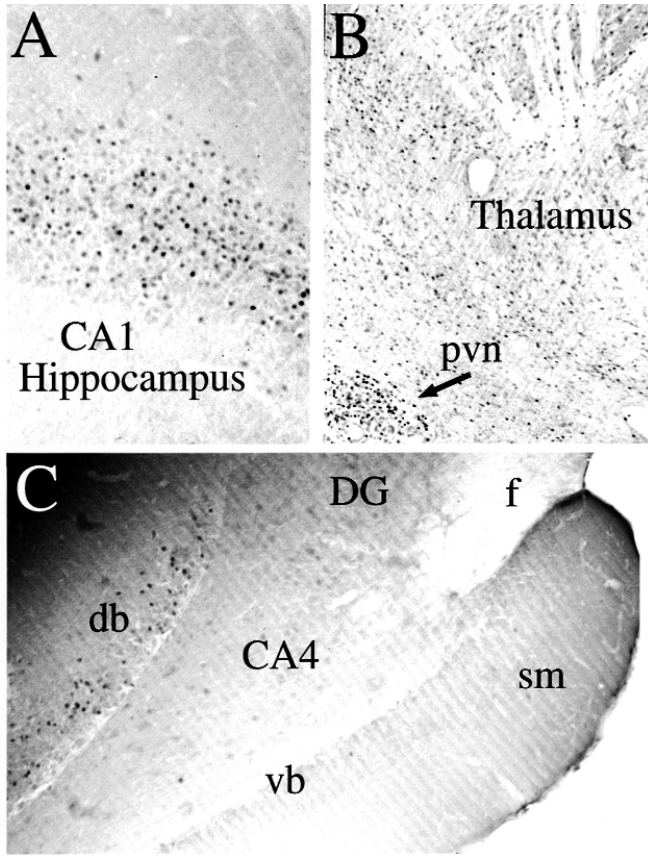


FIG. 7. Activation of c-fos occurs within the hippocampus, primarily in CA1 pyramidal neurons (A) and in neurons of the dorsal blade (db) of the dentate granule cells (C). Fig. 7B. Demonstrates that c-fos is strongly activated in the thalamus and in the hypothalamic paraventricular nucleus (pvn) as well. Abbreviations: CA, cornu ammonis; f, fornix; sm, stratum moleculare; vb, ventral blade; DG, dentate gyms. (Ibogaine treated).

therapeutic actions.

As we have argued elsewhere (*39*), it appears likely that, in rats, an excitatory projection from the deep layers of the neocortex to the neurons of the inferior olive activate their climbing fibers sufficiently to cause excitotoxic damage to the Purkinje neurons that they innervate. This contention is based on the observation that, in mice, ibogaine at 100 mg/kg, i.p. was a completely ineffective neurotoxicant. The only obvious difference in the intensity and pattern of c-fos activation in the mouse, compared to rat, was the striking lack of activation of the

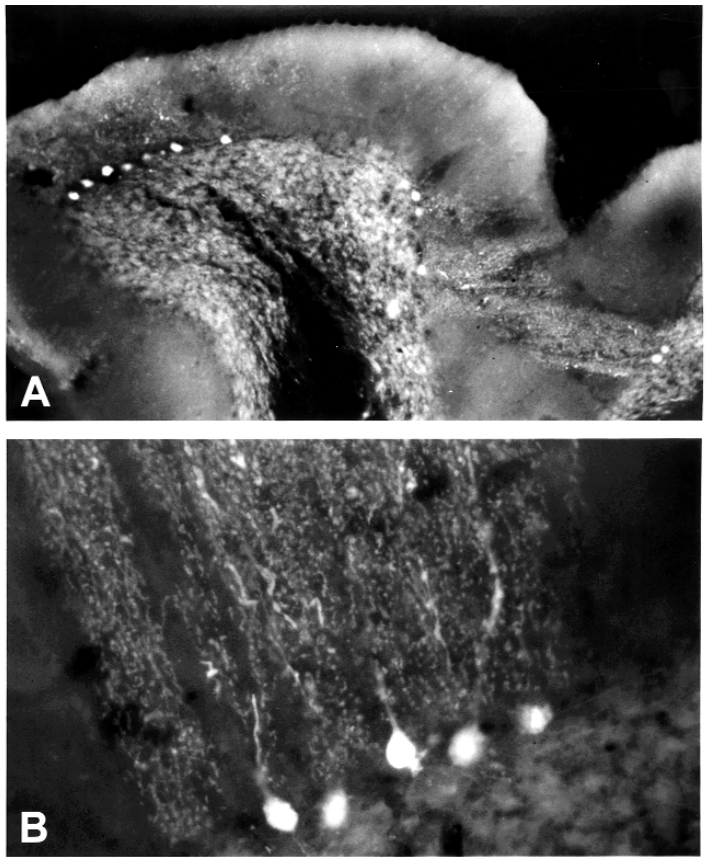


FIG. 8. A. Survey view of the paravermal region of the cerebellum of a rat exposed to ibogaine reveals the patchy distribution of Fluoro-Jade positive degenerating Purkinje cells. B. High magnification view of Fluoro-Jade positive Purkinje cells reveals both cellular and dendritic degeneration while granule cells (lower right) are not labeled.

deeper cortical layers, despite a prominent band demarking a strong excitation of layer 2. These differences between mice and rats may relate to different concentrations of ibogaine-related receptors in their deeper cortical neurons. For more optimal prediction of potential human neurotoxic responses to ibogaine, it might be informative to know if they are more "rat-like" or "mouse-like" in this regard.

In addition to verifying the cerebellar neuropathology using the aforementioned methods of Molliver and O'Hearn, a recently developed marker of neuronal degeneration was also used to validate the previous findings. This marker was Fluoro-Jade, which has been shown to localize neuronal degeneration following a wide variety of insults (*41*). This fluorescent tracer confirmed the existence of small patches of degenerating Purkinje cells. A survey view reveals the patchy appearance of Fluoro-Jade positive cells of the paravermal region of the cerebellum (Figure 8a), while a higher magnification view of these regions reveals the shrunken cytoplasm and extensive dendritic labeling (Figure 8b).

One of the more surprising aspects of ibogaine pathology is the relatively restricted pattern of neuronal degeneration observed. This pattern seen with ibogaine does not obviously correlate with that of neurotoxicants known to act via a specific transmitter system. For example, it is not similar to the distribution of neuropathology commonly associated with either NMDA agonists, which typically involves limbic system degeneration, or NMDA antagonists, which typically involves retrosplenial cortex degeneration (*42,43*). Likewise, there is little similarity to the pattern of degeneration that is observed following dopamine agonists, such as the degeneration in the parietal cortex and midline thalamus seen with methamphetamine, or the pattern that is observed following dopamine toxicants, such as degeneration of neurons of the substantia nigra and dorsal medial thalamus induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)(*44-47*). Inhibitors of oxidative respiration also resulted in a differential pattern of neuronal degeneration. For instance, 3-nitropropionic acid (3-NPA) results in neuronal degeneration within the basal ganglia, medial thalamus, and deep nuclei of the cerebellum (*48,49*). 5-HT agonists may result in a pattern of degeneration most similar to that produced by ibogaine. For example, the 5-HT agonist d-fenfluramine is capable of inducing degeneration of cerebellar Purkinje neurons, as well as neuronal degeneration within frontal cortex and medial thalamus (*44*). This raises the question as to why ibogaine treatment does not also result in degeneration of forebrain structures with a robust serotonergic innervation. One possible explanation is that, like *d*-fenfluramine, hyperthermia may be necessary to potentiate forebrain degeneration. Another possible explanation would be that serotonergic input to glutaminergic forebrain nuclei was not as damaging as the serotonergic input to the aspartate-containing neurons of the brainstem inferior olive.

## IV. Conclusions

Anecdotal reports and published studies in laboratory animals have suggested antiaddictive properties of ibogaine. Ibogaine, like many other indole alkaloids, has hallucinogenic as well as stimulant properties. So the question arose whether treatment of substance addiction with ibogaine may also lead to ibogaine-induced neurotoxicity.

We used electrophysiological, neurochemical, and neurohistological tools to evaluate neurotoxicity of ibogaine. Electrophysiological studies suggest that ibogaine stimulates monoaminergic neurons and may lower the threshold for cocaine induced electrographic seizures. Ibogaine interacts with several neurotransmitter-binding sites, produces significant alterations in neurotransmitter concentrations in different regions of the brain, and also induces immediate early genes (c-fos and erg-1). A single injection of ibogaine produces a spectrum of effects that includes elevation of plasma prolactin and corticosterone, short and long-term effects on dopamine neurotransmission, and modest transient effects on 5-HT. Neuropathological studies reveal that ibogaine administered at high doses produces selective neuronal degeneration. Therefore, we conclude that ibogaine might have potential utility for the treatment of drug addiction, but may also be neurotoxic at high doses, and that more studies are needed to elucidate the apparently complex mechanism of action of this drug.

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