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Ibogaine neurotoxicity: a re-evaluation

H.H. Molinari *, I.M. Maisonneuve, S.D. Glick

Department of Pharmacology and Neuroscience, A-136, Albany Medical College, Albany, NY 12208, USA

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Abstract

Ibogaine is claimed to be an effective treatment for opiate and stimulant addiction. O'Hearn and Molliver, however, showed that ibogaine causes degeneration of cerebellar Purkinje cells in rats. The present study re-examined cerebellar responses to the high doses of ibogaine used by O'Hearn and Molliver (100 mg/kg or 3 × 100 mg/kg) and sought to determine whether a lower dose (40 mg/kg), one effective in reducing morphine and cocaine self-administration, produced similar responses. Purkinje cell degeneration was evaluated with a Fink-Heimer II stain, and enhanced glial cell activity with an antibody to glial fibrillary acidic protein. Every rat treated with the high dose of ibogaine displayed clear evidence of Purkinje cell degeneration. The degeneration consistently occurred in the intermediate and lateral cerebellum, as well as the vermis. Purkinje cells in lobules 5 and 6 were particularly susceptible. Given the response properties of cells in these lobules, this finding suggests any long-term motor deficits produced by ibogaine-induced degeneration should preferentially affect the head and upper extremity. In marked contrast, rats given the smaller dose of ibogaine displayed no degeneration above the level seen in saline-treated animals. When combined with information on other compounds, these data suggest that the degenerative and 'anti-addictive' properties of ibogaine reflect different actions of the drug.

Keywords: Ibogaine; Purkinje cell; Cerebellum; Neurotoxicity; Zebrin; Glial fibrillary acidic protein; Fink-Heimer stain

1. Introduction

Two United States patents (H. Lotsof, 1985, No. 4,499,096; H. Lotsof, 1986, No. 4,587,243) claim that ibogaine can be used as an effective treatment for human opioid (heroin) and stimulant (amphetamine and cocaine) addiction. Many experimental studies in animals lend support to this claim. In rats, for instance, ibogaine decreased self-administration of both morphine [10] and cocaine [2,9]. These studies further showed that ibogaine has long-acting effects: the decreased self-administration lasted 24 h, and sometimes longer, following a single intraperitoneal treatment with 40 mg/kg ibogaine [2,10].

Despite these promising experimental results, studies by O'Hearn et al. and O'Hearn and Molliver [19,20] suggest that ibogaine may be toxic to some parts of the brain. In particular, these studies demonstrated that, in the rat, ibogaine produces degeneration of cerebellar Purkinje cells. Furthermore, ablation of the inferior olive, the source of all climbing fiber inputs to Purkinje cells, appeared to eliminate the ibogaine-induced degeneration [21]. This led O'Hearn and Molliver to propose that the degeneration results from overexcitation of the inferior olive that, in turn, causes excitotoxicity in Purkinje cells.

A number of important issues regarding ibogaine toxicity remain unresolved. First, to produce degeneration of cerebellar Purkinje cells, O'Hearn and Molliver gave rats one to three injections of 100 mg/kg ibogaine. Such doses are at least 2.5 times higher than those that can reduce morphine and cocaine self-administration [2,10]. Thus, these studies did not address the question of whether degeneration is a natural consequence, or possibly even a requirement [23], for the anti-addictive properties of ibogaine. The present study sought to determine whether the lower dose of ibogaine used in the self-administration studies, 40 mg/kg, might cause Purkinje cell degeneration.

Second, O'Hearn and Molliver described the ibogaine-induced degeneration as occurring in longitudinally oriented, parasagittal strips in the cerebellar vermis. This pattern resembles that of the compartmentation of the cerebellum revealed through expression of Zebrin antigens [13]. These authors did not, however, determine whether specific groups of Purkinje cells preferentially respond to ibogaine. Such information could be useful in designing methods of evaluating ibogaine toxicity because it might

* Corresponding author. Fax: +1 (518) 262-5799.

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predict what motor deficits would most likely result from ibogaine-induced degeneration.

Finally, O'Callaghan et al. [18], who measured astrogliosis with an ELISA technique, claim that long-term exposure to ibogaine (14 days) produces markedly different toxic responses in male and female rats. The studies by O'Hearn and Molliver, which examined shorter-term exposure to ibogaine, used only male rats. The present study sought to determine whether ibogaine produces Purkinje cell degeneration in female rats with similar short-term exposures. Because differences in drug sensitivity (and even anatomical connectivity) among animals purchased from different suppliers have been reported [3,11,14], the present study also sought to determine whether ibogaine produces the same toxic response in Sprague–Dawley rats obtained from two different suppliers.

Two approaches were used to evaluate cerebellar responses to ibogaine. First, degeneration of cerebellar Purkinje cells was assessed with the Fink-Heimer II silver stain [7]. This stain selectively impregnates degenerating neuronal elements (as reviewed in [5]). Although it is used primarily to identify degenerating axons and terminals [5], it also readily identifies degenerating Purkinje cell dendrites [6]. Second, glial cell activation was assessed by staining with an antibody to glial fibrillary acidic protein (GFAP). Glial cell activation usually accompanies neuronal injury [19]; conceivably it could indicate a response to ibogaine that does not ultimately lead to overt neuronal degeneration. Finally, to investigate what groups of Purkinje cells were most susceptible to ibogaine, a Zebrin II antibody [13] was used. Portions of this data have been presented in preliminary form [17].

2. Materials and methods

Data were collected from 36 female Sprague–Dawley rats (250–275 g), 16 purchased from Charles River and 20 from Taconic Farms. Experimental animals received intraperitoneal injections of ibogaine hydrochloride (Sigma or RBI) dissolved 10 mg/ml in water. Each received ibogaine in either: (1) a single dose of 40 mg/kg; (2) a single dose of 100 mg/kg; or (3) three doses, one per day for three consecutive days, of 100 mg/kg. Control animals received either no injections or a single intraperitoneal injection of 4 ml/kg saline.

The animals were sacrificed with an overdose of sodium pentobarbital 7, 21, or 26 days after the final drug injection. They were perfused transcardially with 100 USP units of sodium heparin, saline (containing 10% sodium nitrite) and 1000 ml of fixative. The fixative consisted of either 10% formalin or a combination of paraformaldehyde (1% to 4%) and glutaraldehyde (0% to 1.25%) in buffer. The formalin fixative proved to be optimal for the Fink-Heimer processing. A mixed aldehyde fixative was necessary for the immunocytochemical procedures.

The brains were removed from the skull and cryo-protected in sucrose. The cerebella were then separated from the brainstem and cut, with a freezing microtome, in 30 μm-thick, coronal sections. All sections were saved and collected in sets of five. One section from each set of five was stained with Cresyl violet to allow identification of the posterior end of the deep cerebellar nuclei.

Staining for degeneration followed the second Fink-Heimer procedure [7]. Tissue was selected for processing by using the set of five sections containing the posterior end of the deep cerebellar nuclei as a reference point. From this point, sections 900 μm apart (i.e. from every sixth set of five) were chosen until the entire anterior–posterior extent of the cerebellum was sampled. This selection procedure insured that in every animal all cerebellar lobules were systematically evaluated.

The Fink-Heimer stain can be capricious. Therefore, sections from one of the first two animals examined (animal Ib2) were used as controls for all Fink-Heimer staining; in this animal tissue preservation was ideal and the cerebellum clearly contained degeneration. These control sections were processed along with all other tissue. If degeneration was not apparent in the control sections, the Fink-Heimer procedure was repeated on another set of sections.

Immunocytochemical staining largely followed O'Hearn et al. [19] for GFAP and Gravel and Hawkes [12] for Zebrin. A mouse monoclonal GFAP antibody (Sigma) was diluted 1:20000; the anti-Zebrin II antibody (kindly provided by Dr. R. Hawkes) was diluted 1:250. Both were revealed with a Vectastain ABC kit and diaminobenzidine. One section from each set of five was processed with antibody, producing staining in sections 150 μm apart, which sampled the entire anterior–posterior extent of the cerebellum.

To determine the distribution of responses to ibogaine, sections from the cerebellum were projected at a magnification of 23 × onto a sheet of paper. For each section, the edge of the section, the Purkinje cell layer, and the locations of either degeneration (Fink-Heimer stained tissue) or of enhanced GFAP staining (GFAP-stained tissue) were drawn. The sections were then examined at 100 × with a light microscope. Any missed responses to ibogaine were manually added using tissue landmarks to insure proper placement.

3. Results

3.1. Identification of ibogaine response in cerebellum

Desclin [6] noted that Purkinje cell degeneration in Fink-Heimer stained, coronal sections appears as rows of coarse silver granules that follow the orientation of the Purkinje cell dendrites. The rows extend from the Purkinje cell layer through the molecular cell layer to the surface of

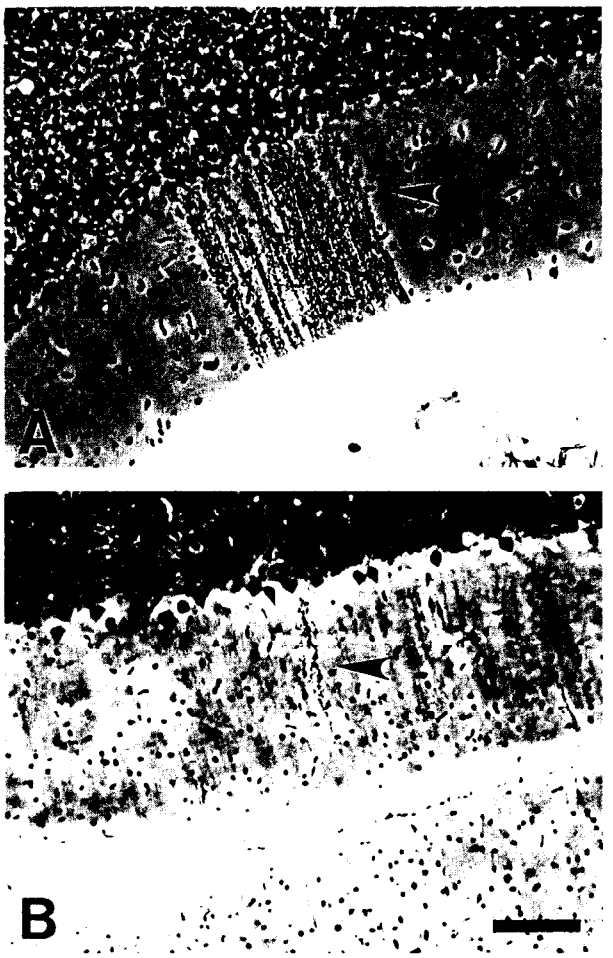

Fig. 1. Fink-Heimer stained tissue from an animal treated with 3×100 mg/kg ibogaine (A) and an animal treated with 40 mg/kg ibogaine (B). Sections are oriented with the granule cell layer (dark) on top and the molecular cell layer (light) below. In B, the Purkinje cell layer can be seen as a single row of black Purkinje cell bodies between the granule and molecular cell layers. In both micrographs, degenerating Purkinje cell dendrites (arrowheads) appear as longitudinally oriented rows of silver grains that extend across the molecular cell layer. The bar represents 100 μm and applies to A and B.

the cerebellum. In the present study, the staining patterns in animals allowed to survive seven days occurred in two forms: (1) bands of granules of varying thickness (Fig. 1A) that appeared to represent groups of degenerating Purkinje cells; and (2) isolated single lines of granules (Fig. 1B) that appeared to represent either single degenerating Purkinje cells or artifactual staining. It was not possible to differentiate between the latter two possibilities. Therefore, the isolated lines were conservatively classified as single degenerating Purkinje cells.

Over time, degenerating, silver-stained neurons are phagocytosed [15]. Thus, in animals with the longer survival times, degeneration appeared much less often than in animals allowed to survive seven days. Furthermore, degeneration found at longer survival times occurred only in those locations where the greatest amounts of degeneration occurred at the shorter survival time. No new areas of staining were revealed. As a result, the presentation below is limited solely to data from animals allowed to survive seven days.

In GFAP-stained sections, responses to ibogaine consisted of areas of intense staining with the same locations, orientation, and width as the bands and lines in the Fink-Heimer stained tissue. Therefore, the intense GFAP-stained areas were also classified as indicating responses to ibogaine either by groups of Purkinje cells or by single isolated Purkinje cells.

3.2. Response to high doses of ibogaine

Every animal treated with either one or three doses of 100 mg/kg ibogaine and allowed to survive seven days displayed clear evidence of Purkinje cell degeneration. Characteristically the degeneration occurred in bands similar to the one shown in Fig. 1A. Fig. 2 illustrates the distribution of degeneration in two different animals treated with 3 × 100 mg/kg ibogaine. For both animals, the sections shown sample all of the cerebellar lobules: the top section illustrates the posterior lobe of the cerebellum; the middle section, the region where the deep cerebellar nuclei are most developed; and the bottom section, primarily the anterior lobe. Because tissue from animal Ib2 (Fig. 2, left) was used as a degeneration control, Fink-Heimer processing was carried out for every section from the cerebellum of this animal. Examination of sections from the rest of the cerebellum from animal Ib2 showed that Fig. 2 presents a representative picture of the ibogaine-induced degeneration in this animal, in that no significant new areas of staining occurred in other sections.

From Fig. 2 it is apparent that there was considerable animal-to-animal variability in the amount of degeneration. Thus, it appears that the response to ibogaine was not stereotyped. Nevertheless, the patterns of degeneration in the two animals shown in Fig. 2 displayed several common features. First, in the bottom two sections for each animal, the degeneration formed continuous bands that extended through multiple lobules (arrows). Second, the degeneration displayed a high degree of bilateral symmetry. In fact, the apparent lack of symmetry in some sections (i.e. the top two of Fig. 2) probably reflects the fact that the sections themselves could not always be cut symmetrically due to the curvature of the cerebellum. Third, some lobules appeared more susceptible to the effects of ibogaine than others.

To determine whether the lobule-specific susceptibility suggested by Fig. 2 holds in general, the degeneration in all animals treated with 3 × 100 mg/kg ibogaine and allowed to survive 7 days was quantified. This was done by classifying each lobule as containing degeneration if, in a single section, it contained either a band of degeneration or a minimum of two isolated lines of degeneration (as

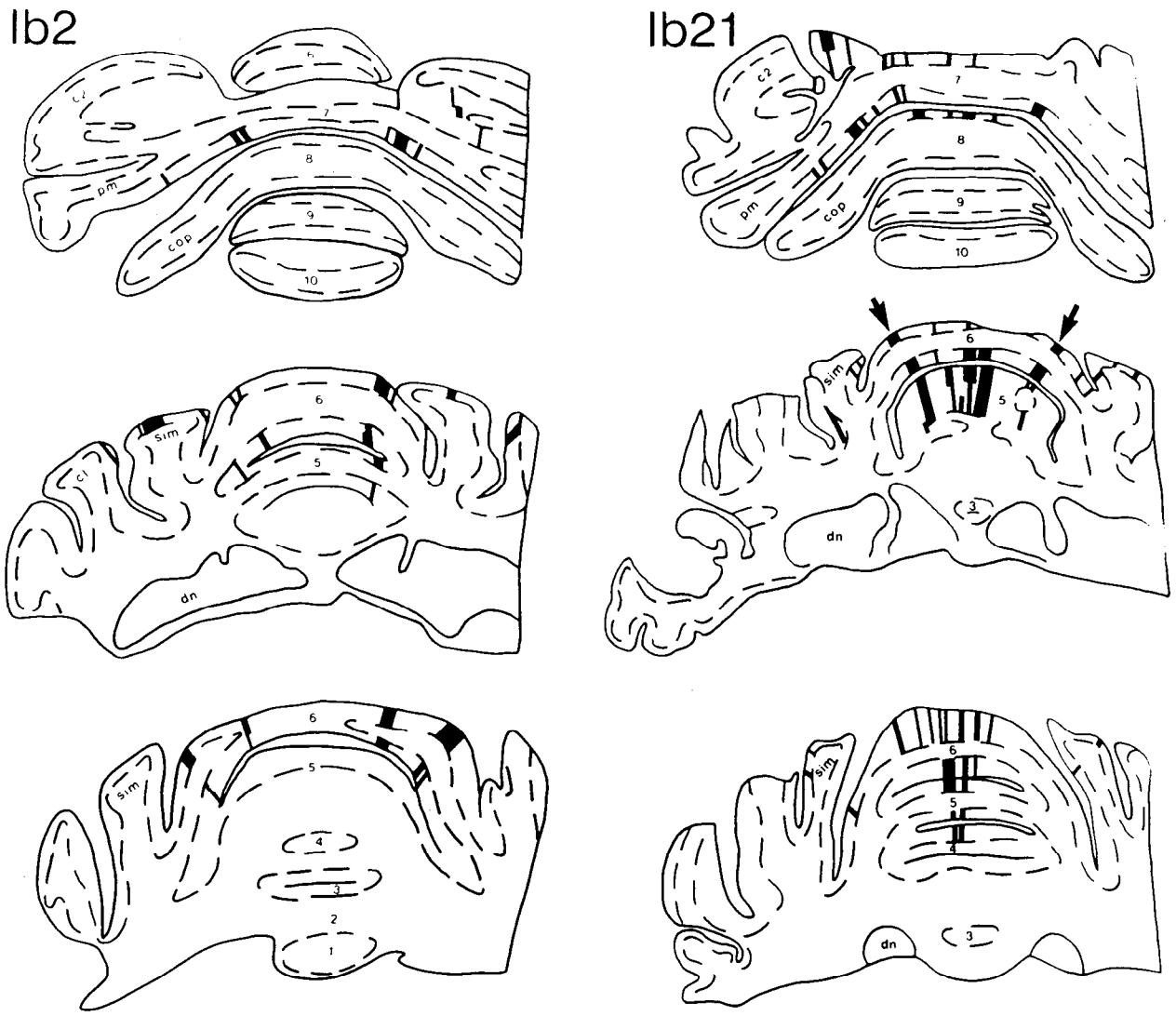

Fig. 2. The distribution of degeneration in three Fink-Heimer-stained sections from two different animals (Ib2 and Ib21) treated with 3 × 100 mg/kg ibogaine. For both animals, the right edge of the cerebellum was removed prior to sectioning in order to allow orientation of the sections. Dashed lines indicate the location of the Purkinje cell layer; solid black bars oriented perpendicular to the dashed lines indicate the locations of degenerating Purkinje cell dendrites. The arrows indicate two bilaterally symmetric bands of degeneration. Cerebellar lobules are labeled by numbers 1 through 10 and the abbreviations c1 (crus 1), c2 (crus 2), cop (copula), pm (paramedian), and sim (simplex); the deep cerebellar nuclei are labeled dn.

discussed below, the minimum of two allowed differentiation between normally occurring and unusual amounts of degeneration). Fig. 3 presents the results from 10 animals.

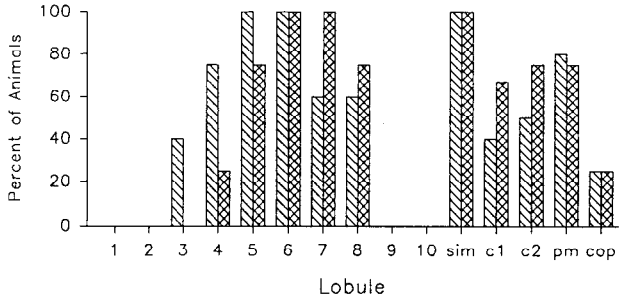

Fig. 3. The distribution of degeneration across cerebellar lobules in all animals treated with 3 × 100 mg/kg ibogaine. Data were collected from 6 Charles River animals (diagonal shading) and 4 Taconic Farms animals (cross hatching). Cerebellar lobules are identified as in Fig. 2.

This figure shows that in virtually every animal degeneration occurred in four lobules, 5, 6, 7 and simplex (sim). On the other hand, in no animals did degeneration occur in lobules 1, 2, 9, and 10. Although the sample size was smaller, a similar pattern occurred in animals given a single dose of 100 mg/kg ibogaine. This suggests that the size of the dose has more influence than the number of doses in determining toxicity.

Fig. 3 also shows that the distribution of degeneration varied little across animals obtained from different suppliers. Thus, although the amount of degeneration may vary considerably from animal to animal, the source of the animal appeared to have no significant impact.

Examination of Fig. 3 also reveals that degeneration consistently occurred in lateral portions of the cerebellum. That is, the laterally placed simplex lobule contained degeneration in every animal; the crus 2 (c2) and paramedian

(pm) lobules contained degeneration in at least half of the animals. Thus responses to ibogaine were not confined to the vermis (the medial portion) of the cerebellum, as suggested by O'Hearn et al. and O'Hearn and Molliver [19,20]. In addition, comparison of GFAP and Zebrin staining patterns indicated that responses to ibogaine in lobules 5 and 6 routinely extended laterally out of the vermis and into pars intermedia (as defined by Voogd et al. [24]).

As noted earlier, GFAP staining revealed responses to ibogaine very similar to those demonstrated with the Fink-Heimer procedure. In particular, GFAP staining occurred in parasagittal bands like those shown in Fig. 2. The Zebrin antibody also revealed parasagittal bands. As described previously [13], Zebrin bands in the anterior lobe extended continuously from lobule 6 into lobule 1. In contrast, GFAP bands in the same animals extended onl into lobule 3. Thus, there is no one-to-one correspondenc between Purkinje cells that contain the Zebrin antigen an those susceptible to ibogaine.

3.3. Response to a low dose of ibogaine

According to Desclin [6], isolated lines of Fink-Heime staining, such as in Fig. 1B, occur sporadically in norma untreated animals. As can be seen from Fig. 4, the preser study confirmed this observation: in the saline-treated an mal (Ib11, left), only four isolated lines of silver grain occurred in the 13 lobules shown. Similar isolated line also occurred in animals treated with 40 mg/kg ibogaine the sections from animal Ib14 shown on the right of Fig. contained only five isolated lines in the same number c

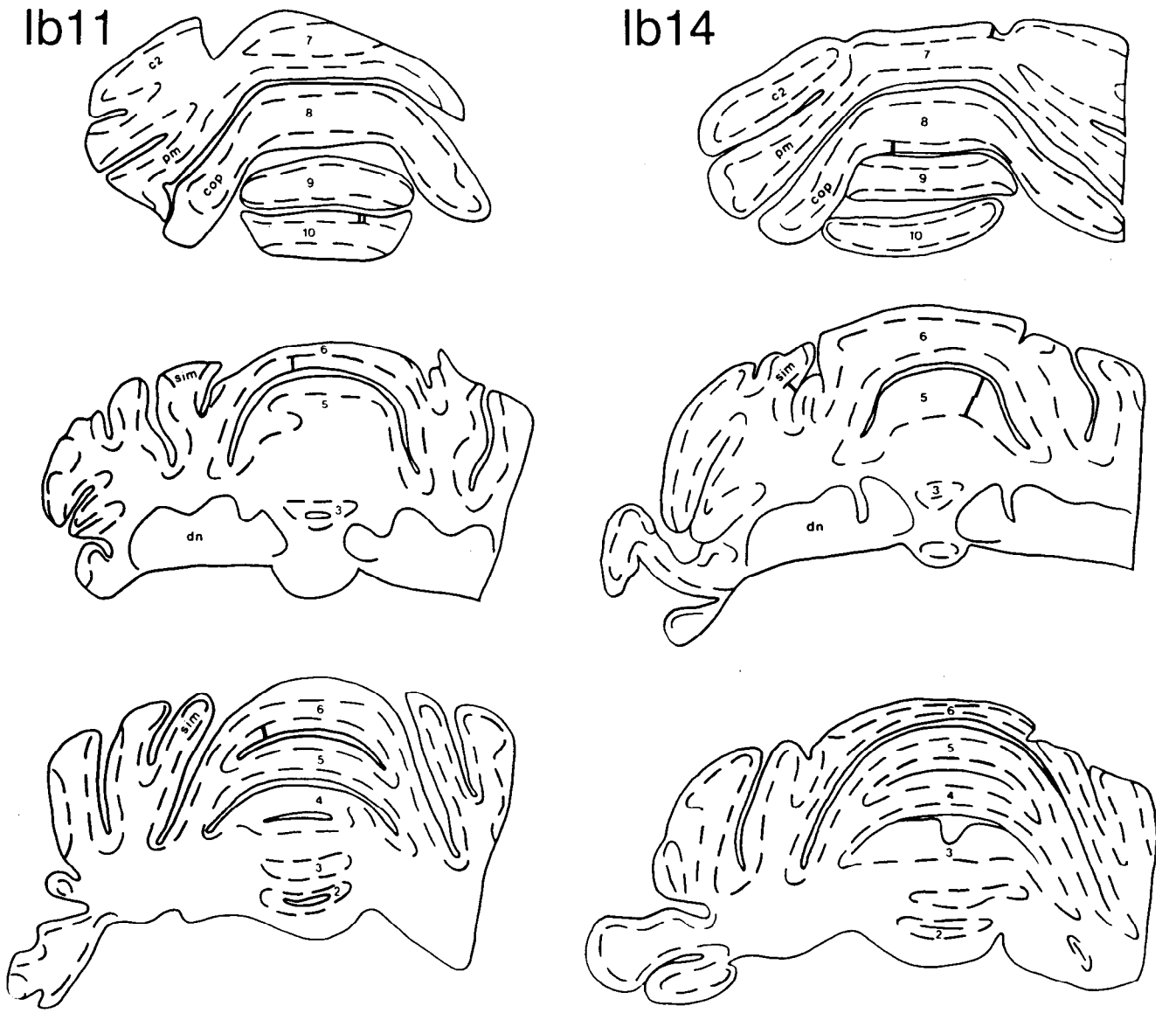

Fig. 4. The distribution of degeneration in an animal treated with saline (Ib11) and an animal treated with 40 mg/kg ibogaine (Ib14). Sections wer processed, drawn, and labeled as in Fig. 2.

lobules. Most importantly, the bands of degeneration (Fig. 1A) readily found in animals treated with high doses of ibogaine were never encountered in animals treated with either saline or a low dose of ibogaine.

The difference between animals treated with 40 mg/kg vs. 3 × 100 mg/kg ibogaine can readily be appreciated by comparing Figs. 2 and 4. In order to allow comparison across all animals, it would have been desirable to obtain some quantitative measure of the proportion of the cerebellum showing degeneration in each animal. Because of the curvature and convolutions of the cerebellar cortex, it is not possible to cut all Purkinje cell dendrites in the same plane, i.e. the dendrites intersect the cutting plane at every possible angle. Dendrites lying entirely in the plane of section would form longer bands of degeneration than dendrites that intersected the plane of section at some angle. As a result, estimates of the number of degenerating Purkinje cells, rather than the proportion of cerebellum covered by degeneration, would provide the only meaningful measure for inter-animal comparisons of degeneration produced by different doses of ibogaine.

Qualitatively all but one animal could readily be placed in one of two categories by estimating the number of degenerating Purkinje cells. Animals were classified as having extensive degeneration if the tissue contained multiple, bilaterally symmetric bands of Fink-Heimer or GFAP staining in both the anterior and posterior lobes of the cerebellum. Animals were classified as lacking degeneration if the tissue contained two or fewer isolated lines of degeneration per section (i.e. an average of considerably less than one per lobule).

Table 1 shows the classifications for all animals treated with the different doses of ibogaine. From this table it is clear that doses of 100 mg/kg ibogaine (given once or three times) produced degeneration in every animal tested.

Table 1
The occurrence of degeneration in all animals examined

Source	Tissue stin	No degeneration	Degeneration
Animals treated with saline			
Charles River	Fink-Heimer	2	0
Animals treated with 40 mg/kg ibogaine			
Charles River	Fink-Heimer	5	0
	GFAP	2	0
Taconic Farms	Fink Heimer	5	1 *
	GFAP	2	0
Animals treated with 100 mg/kg ibogaine			
Taconic Farms	Fink-Heimer	0	2
Animals treated with 3 × 100 mg/kg ibogaine			
Charles River	Fink-Heimer	0	4
	GFAP	0	2
Taconic Farms	Fink-Heimer	0	5

* The degeneration in this animal was minimal and confined to lobules 6 and 7.

A dose of 40 mg/kg, on the other hand, generally only produced the same low level of degeneration as saline treatment. Only one of the fifteen animals treated with 40 mg/kg ibogaine displayed evidence of degeneration at a level greater than that seen in saline-treated animals. The amount of degeneration in this animal did not, however, come close to that seen with high doses of ibogaine. In particular, the degeneration consisted only of isolated lines of silver grains scattered across lobules 6 and 7.

Table 1 further shows that in animals treated with 40 mg/kg, GFAP staining revealed no greater incidence of responses to ibogaine than did Fink-Heimer staining. Thus, 40 mg/kg ibogaine appears to have little or no adverse effect on the cerebellum, for either of the staining procedures tested.

4. Discussion

This study confirms the observations of O'Hearn et al. and O'Hearn and Molliver [19,20] that high doses of ibogaine produce degeneration of cerebellar Purkinje cells. It further extends these observations by showing that degeneration (1) occurs in female as well as in male rats; (2) does not differ across animals purchased from different suppliers; and (3) consistently occurs in intermediate and lateral portions of the cerebellum, as well as in the vermis.

The specific groups of Purkinje cells that degenerate in response to high doses of ibogaine varied markedly from animal to animal. In Fig. 2, for instance, the area around the midline of one animal (Ib21) contained numerous bands of degeneration whereas the same area in the other animal (Ib2) contained none. Similarly, the 'anti-addictive' properties of ibogaine display marked intersubject variability [9].

Despite the lack of a stereotyped response across animals, certain cerebellar lobules preferentially responded to high doses of ibogaine. In the anterior lobe, for instance, degeneration occurred always in lobules 5 and 6, never in lobules 1 and 2, and occasionally in lobules 3 and 4. As in most species, the rat anterior lobe displays a topographic organization: Purkinje cells responsive to stimulation of the forelimb and face are concentrated in the vermis and intermediate portions of lobules 5 and 6; Purkinje cells responsive to stimulation of the hindlimb, on the other hand, extend from lobules 2 to 6 [16]. As a result, ibogaine should have the most profound impact on movements of the head and upper extremity. During the first hour following administration of ibogaine, rats and mice consistently display tremor (e.g. [25]); **a recent study found that this tremor preferentially involves the head and upper extremity** [4]. The nature of any longer-term deficits produced by ibogaine toxicity is not known. Casual examination of the animals in the present study given high doses of ibogaine revealed no gross motor deficiencies on the day they were

sacrificed. The results of this study suggest, however, that any evaluation of the possible long-term toxic effects of ibogaine should look for subtle motor deficits in movements of the head or upper extremity rather than irregularities in gait.

High doses of ibogaine readily produced degeneration of cerebellar Purkinje cells. In marked contrast, a low dose of ibogaine failed to produce, in female rats, either degeneration of cerebellar Purkinje cells or responses in glial cells beyond those in saline-treated animals. Male rats were not included in the present study. The fact that female rats are more sensitive to the behavioral effects of ibogaine than males [22], however, suggests that males would be even less likely to display toxic responses. For either gender, the low dose of ibogaine does display 'anti-addictive' properties [2,9,10]. Thus, it appears that alteration of addictive behavior by ibogaine does not require degeneration of cerebellar Purkinje cells.

Recent work shows that 18-methoxycoronaridine, an *iboga* alkaloid congener, has 'anti-addictive' properties but does not cause Purkinje cell degeneration, even at high doses [8]. Unlike ibogaine, 18-methoxycoronaridine does not cause tremor [8]. Moreover, compounds such as harmaline readily produce both tremor [25] and Purkinje cell degeneration [20] but have no long-term impact on morphine or cocaine self-administration [9]. These data support a growing body of evidence [9] indicating that although ibogaine and related compounds can produce degeneration in the cerebellum, this degeneration reflects their tremorigenic rather than their 'anti-addictive' properties. The tremors result, at least in part, from synchronous activation of neurons in the inferior olive [1]. It appears that only when activation of the inferior olive reaches extreme levels, causing vigorous tremors [19], does loss of cerebellar Purkinje cells occur. The level of activation of the inferior olive and cerebellum appears, however, to have no bearing on the ability of ibogaine to influence addictive behavior. This suggests that, in contrast to the proposal of O'Hearn and Molliver [23], the cerebellum does not play a role in addiction.

Acknowledgements

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