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Effects and aftereffects of ibogaine on morphine self-administration in rats

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Ibogaine, a naturally occurring alkaloid, has been claimed to be effective in treating addiction to opiate and stimulant drugs. As a preclinical test of this claim, the present study sought to determine if ibogaine would reduce the intravenous self-administration of morphine in rats. Ibogaine dose dependently (2.5-80 mg/kg) decreased morphine intake in the hour after ibogaine treatment (acute effect) and, to a lesser extent, a day later (aftereffect); while the acute effect could be attributed to abnormal motor behavior (whole body tremors), the aftereffect occurred at a time when ibogaine should have been entirely eliminated from the body and when there was no obvious indication of ibogaine exposure. In some rats, there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine; other rats began to show such persistent changes only after two or three weekly injections whereas a few rats were apparently resistant to prolonged aftereffects. Aftereffects could not be attributed to a conditioned aversion. Although ibogaine also depressed responding acutely in rats trained to bar-press for water, there was no evidence of any aftereffect a day or more later; the interaction between ibogaine and morphine reinforcement was therefore somewhat specific. Further studies are needed to characterize the nature of the ibogaine-morphine interaction as well as to determine if ibogaine also affects the self-administration of other drugs.

Ibogaine; Morphine; Drug self-administration

1. Introduction

Ibogaine is one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*. Extracts of iboga have a long history of use, principally as a stimulant to keep African hunters awake and motionless while stalking prey but also as part of initiation rites and religious rituals of Bwiti and Mbiri cults. Studies conducted in France in the early part of this century indicated that ibogaine had hallucinogenic as well as stimulant properties. Although never widespread in the USA, ibogaine's appearance on the illicit market in the 1960s caused the FDA (Food and Drug Administration) in 1970 to classify it as a Schedule I substance (all non-research use forbidden). More recently, two United States patents, numbers 4,499,096 (Feb. 12, 1985) and 4,587,243 (May 6, 1986), have described the potential efficacy of ibogaine in treating opiate (heroin) addiction and stimulant (cocaine and amphetamine) abuse, respectively. In both opiate and stimulant syndromes, a single oral treatment of ibogaine or its salts in dosages of 6-19 mg/kg was claimed to be effective for about six

months. The treatment supposedly interrupted the 'physiological and psychological aspects' of addiction and eliminated the desire to use drugs; a series of four treatments was said to be effective for approximately three years. Using an animal model of drug addiction, we have sought to determine whether these claims can be substantiated under controlled conditions. In the present study, the effects of single and, in some cases, repeated injections of ibogaine on rates of morphine self-administration in rats were assessed for several days after ibogaine treatment. Though far from addressing the full extent of the claims presented in the patents, the results of this study suggest that such claims should be taken seriously and that further investigation is warranted.

2. Materials and methods

2.1. Subjects and apparatus

The subjects were naive female Sprague-Dawley (Taconic, Germantown, NY) rats approximately three months old and weighing 230-250 g at the beginning of the experiment. Rats were housed singly in Wahmann hanging cages and maintained on a normal light/dark cycle (lights on/off at 7:00 a.m./7:00 p.m.). All testing

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was conducted in six BRS/LVE operant test cages, each enclosed in a sound-attenuated cubicle. Responses on either of two levers in each test cage were recorded on Sodeco counters. The intravenous (i.v.) self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks (1972), BRS/LVE harnesses and commutators, and Harvard Apparatus infusion pumps (No. 55-2222).

2.2. Procedure

Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks (1972). Self-administration testing began with a single 24 h session followed by daily 1 h sessions, five days (Monday-Friday) a week; rats were tested about the same time each day, during the middle of the light cycle. A response on either lever produced a 10 μ l infusion of drug solution, 0.01 mg of morphine sulfate, in about 0.2 s. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine; this is about four times the threshold dose required for maintaining self-administration behavior (e.g. Glick and Cox, 1977). One non-contingent drug infusion was administered at the beginning of each session. It should be noted that the daily 1 h test sessions were not sufficient to produce any observable degree of physical dependence; there were no symptoms of withdrawal (e.g. weight loss, diarrhea, wet dog shakes) during abstinent periods (i.e. weekends). Experiments to assess the effects of ibogaine were begun when baseline self-administration rates stabilized ($\leq 10\%$ variation from one day to the next across five days), usually after two weeks of testing.

Ibogaine hydrochloride was purchased from the Sigma Chemical Company (St. Louis, MO); doses, ranging from 2.5 to 80 mg/kg, are expressed as the salt. Ibogaine (or saline) was administered intraperitoneally (i.p.); different doses were administered to different groups of rats. Most rats were injected 15 min before a morphine self-administration session (pre-session treatment) while some rats were injected within 5 min after such a session (post-session treatment). Ibogaine injections were usually made on Wednesdays and, in some cases, repeated injections were made at weekly or bi-weekly intervals. In order to provide an indication of the specificity of ibogaine's effects on bar-pressing for morphine, ibogaine (40 mg/kg) was also administered pre-session to other rats bar-pressing for water.

3. Results

Figure 1 shows the initial acute effects of pre-session ibogaine treatment on morphine self-administration.

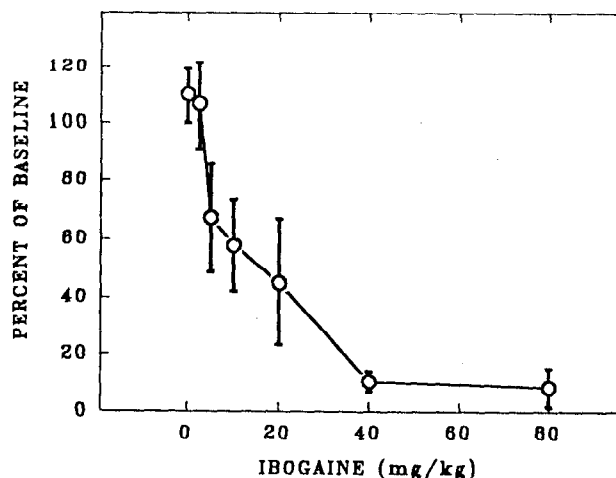


Fig. 1. Acute effects of ibogaine on morphine self-administration. Each data point is the mean (\pm S.E.) from 4-12 rats. Baseline was calculated as the average rate for the three sessions preceding ibogaine or saline (0 mg/kg) treatment. Doses of 10 mg/kg and higher had significant effects (ANOVA and t-tests, $P < 0.05-0.001$).

Ibogaine produced a dose-related depression of morphine intake (ANOVA, $P < 0.001$); doses of 10 mg/kg and higher had significant ($P < 0.05-0.001$, t-tests) effects.

Figure 2 shows that both pre-session and post-session ibogaine (40 mg/kg) treatment, administered for the first time, depressed morphine intake for at least a day afterwards. A group \times days interaction was significant ($P < 0.02$) in a two-way ANOVA; paired t-tests with baseline values were significant ($P < 0.05-0.001$) for days 1 and 2 in the pre-session group and for day 2

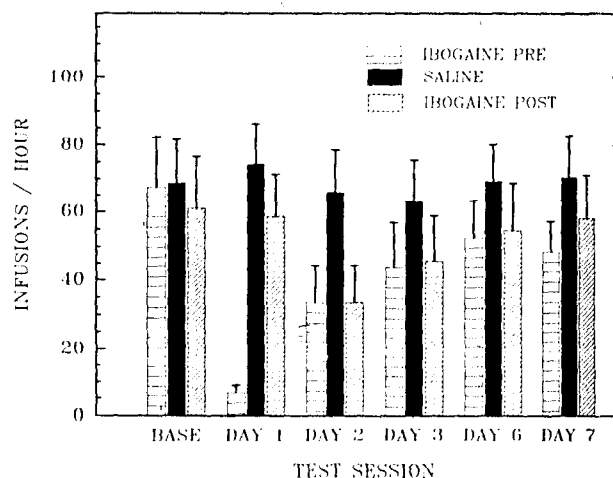


Fig. 2. Aftereffects of ibogaine (40 mg/kg) on morphine self-administration: pre- versus post-session administration on day 1. Each data point is the mean (\pm S.E.) from 6-11 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding ibogaine or saline treatment. There were significant effects on days 1 and 2 for pre-session treatment and on day 2 for post-session treatment (ANOVA and t-tests, $P < 0.05-0.001$).

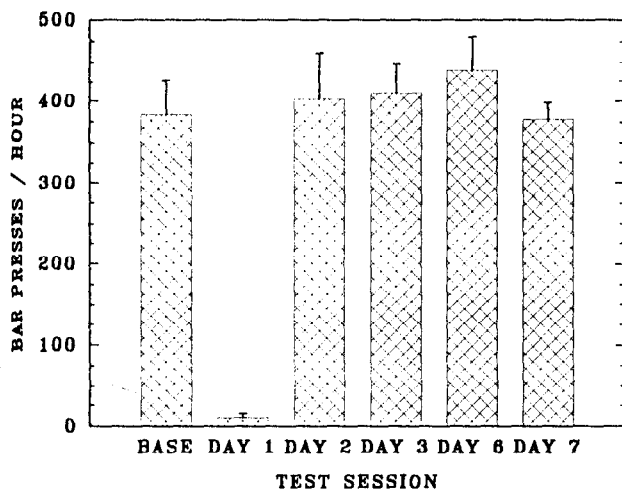


Fig. 3. Lack of aftereffects of ibogaine (40 mg/kg) on bar-pressing for water: pre-session administration on Day 1. Each data point is the mean (\pm S.E.) from six rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding ibogaine treatment. There was a significant ($P < 0.001$, t-test) effect on day 1 but not thereafter.

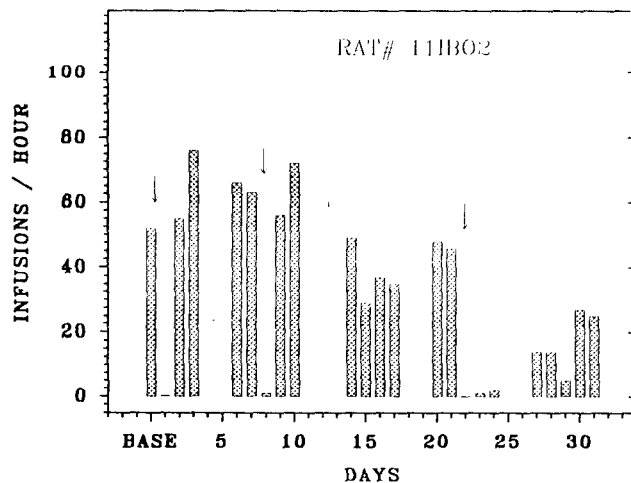


Fig. 5. Individual response to repeated injections of ibogaine (40 mg/kg, pre-session) on morphine self-administration: rat No. 111B02 treated (arrows) on days 1, 8 and 22; aftereffects only became apparent after the third injection.

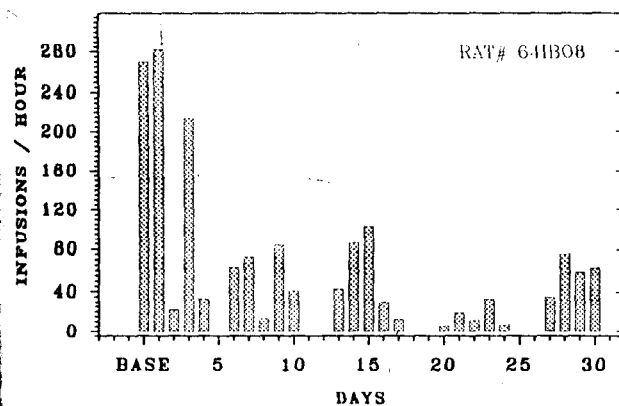
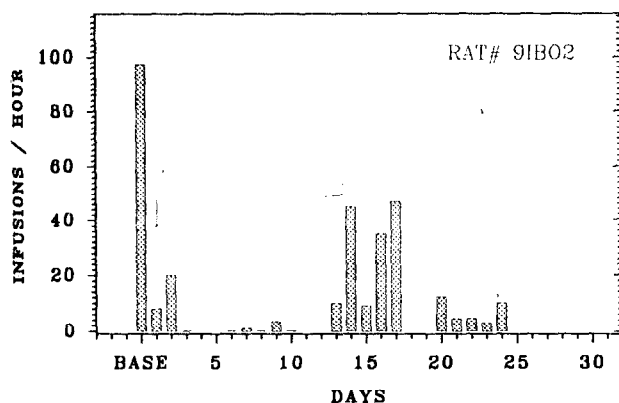


Fig. 4. Long-term aftereffects of ibogaine on morphine self-administration in two rats: rat No. 91B02 treated (indicated by arrow) with 40 mg/kg pre-session on day 1 and rat No. 641B08 treated with 80 mg/kg post-session on day 1.

in the post-session group. Figure 3 shows that pre-session ibogaine (40 mg/kg) treatment decreased bar-pressing for water only acutely, there being no effect a day later.

The aftereffects (one or more days later) of ibogaine on morphine self-administration varied substantially from rat to rat. In almost all instances (see exception below, rat No. 111B02), doses of 40 and 80 mg/kg (but not 10 or 20 mg/kg) depressed intake a day later; however, thereafter, responses ranged from no further effect to a prolonged depression of morphine intake, lasting, in some cases, for several weeks. Figure 4 shows two examples of the latter—one rat (No. 91B02) administered 40 mg/kg pre-session and another rat (No. 641B08) administered 80 mg/kg post-session. When such aftereffects were not apparent for particular rats, repeated injections of ibogaine were made, usually at weekly or biweekly intervals. Figure 5 shows data of a rat (No. 111B02) that was administered ibogaine (40 mg/kg, pre-session) three times: on the first two occasions there were no obvious effects beyond the day of injection whereas, after the third injection of ibogaine, morphine intake was clearly depressed for at least a week afterwards. Some rats showed prolonged aftereffects following a second injection whereas others showed no aftereffects lasting more than a day even following five injections of ibogaine.

4. Discussion

Ibogaine produced an acute dose-related depression of morphine self-administration. This may have oc-

curred for one of several reasons; for example, while ibogaine may have specifically affected the reinforcing efficacy of morphine, it also may have more generally interfered with the motor behavior necessary to perform the operant response. As is well known (e.g. Zetler et al., 1972), ibogaine elicits whole body tremors and these may have made it difficult or impossible to execute any coordinated motor response. The acute depression of bar-pressing for water by ibogaine would also be consistent with the latter interpretation. It should be noted, however, that aside from tremors, no other signs of overt toxicity were observed.

The half-life of ibogaine in rodents is about 1 h (Dhahir, 1971) and, a day after administration, ibogaine levels in the body should be undetectable (Dhahir, 1971). Inasmuch as ibogaine-induced tremors disappeared within 2-3 h after a dose of 40 mg/kg, it was somewhat remarkable that rates of morphine self-administration were still significantly decreased a day later (fig. 2). It seemed conceivable that such an effect might have occurred as a result of an associative process. That is, pretreatment with ibogaine might have made morphine aversive and the persistence of a decrease in morphine intake could then have been due to a conditioned aversion (i.e. a conditioned decrease in bar-pressing); rats administered ibogaine after testing for morphine self-administration (post-session treatment) were included to evaluate this possibility. Ibogaine had the same effect a day later regardless of whether it had been administered before or after the morphine self-administration session. The specificity of this aftereffect on morphine intake was further indicated by the observation that the same dose of ibogaine had no effect beyond the day of administration in rats bar-pressing for water (fig. 3). Thus, in contrast to its acute rate-depressant effect, the day-later aftereffect of ibogaine on morphine self-administration appears to have resulted from some persistent modulatory action of ibogaine on the reinforcing efficacy of morphine.

Long-term decreases in morphine intake lasting for several days and in some cases for several weeks after ibogaine (40 or 80 mg/kg) treatment occurred in some rats. It was not possible to predict which rats would respond in this way, although there was a non-significant trend for rats having low baseline rates of drug intake to be less likely to exhibit such effects. When ibogaine treatments were repeated at weekly or bi-weekly intervals, some rats that were initially resistant began to show long-term aftereffects; this suggests that there is a continuum of individual differences in sensitivity to ibogaine and that, with some dosage regimen, most or all rats would show long-term depressions of morphine intake.

Possible mechanisms underlying ibogaine's aftereffects are at present obscure. Very little is known about the metabolism of ibogaine although there is no reason

to exclude the possibility that there is an active metabolite with a long half-life. Ibogaine and related drugs (e.g. tabernanthine) have been suggested to have several neuropharmacological actions, including interactions with serotonergic (Sloviter et al., 1980), muscarinic (Dhahir, 1971) and benzodiazepine receptors (Trouvin et al., 1987); although there is no evidence of a direct interaction at opiate receptors, ibogaine has been reported to potentiate the analgesic effect of morphine (Schneider and McArthur, 1956). None of these mechanisms have been shown or even been suggested to be operative for more than a few hours after ibogaine administration. In contrast, as reported in our companion paper (Maisonneuve et al., 1991), ibogaine induces prolonged (at least 19 h) decreases in the extracellular levels of dopamine metabolites (DOPAC and HVA) in the nucleus accumbens, striatum and medial prefrontal cortex; although the cellular basis for these effects is also not understood, the microdialysis data are certainly consistent with the present self-administration data in terms of the well documented role of dopaminergic systems in morphine reinforcement (e.g. Wise, 1987; Wise and Bozarth, 1987).

Assuming that ibogaine alters the reinforcing efficacy of morphine, the ibogaine-induced decrease in morphine intake could result from either antagonism or enhancement of morphine's actions (e.g. Glick and Ross, 1983). That is, if ibogaine antagonized morphine's actions, it would be expected that rats might transiently self-administer more morphine in an attempt to compensate for the reduced effect but then self-administer less morphine as extinction occurred (i.e. analogous to decreasing the morphine infusion dose to below threshold); if ibogaine enhanced morphine's actions, it would be expected that rats would also self-administer less morphine but, in this case, as a way of compensating for the increased effect (i.e. analogous to increasing the morphine infusion dose). Although there was no evidence of a biphasic extinction pattern of responding that would support the 'antagonist' interpretation, other treatments (e.g. lesions) that disrupt drug self-administration by reducing reinforcing efficacy frequently do so without producing an initial increase in responding (e.g. Roberts and Koob, 1982). It is therefore not possible to discriminate between these two interpretations on the basis of the present data alone. Further studies are clearly warranted to address this issue as well as to explore the generality of the present findings with respect to ibogaine's claimed interactions with other drugs of abuse.

Acknowledgement

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