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Effects of harmane and other β-carbolines on apomorphine-induced licking behavior in rat

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ABSTRACT

Harmane, harmine and norharmane are β-carboline compounds which have been referred to as inverse agonists of benzodiazepine receptors. The effect of these compounds on apomorphine-induced licking behavior was studied in rats. Subcutaneous (s.c.) injection of apomorphine (0.5 mg/kg) induced licking. The licking behavior was counted with a hand counter and recorded for a period of 75 min by direct observation. Intraperitoneal (i.p.) injections of harmane (1.25–5 mg/kg), harmine (2.5–10 mg/kg) and norharmane (1.25–5 mg/kg) significantly reduced the licking behavior. In rats pretreated with reserpine (5 mg/kg, i.p., 18 h before the test), the effects of harmane (4 mg/kg, i.p.), harmine (7.8 mg/kg, i.p.) and norharmane (2.5 mg/kg, i.p.) were unchanged. When flumazenil (2 mg/kg, i.p.) was administered 20 min before apomorphine, it was able to antagonize the effects of harmane, harmine and norharmane. It was concluded that the β-carbolines harmane, harmine and norharmane reduce the licking behavior via an inverse agonistic mechanism located in the benzodiazepine receptors.

1. Introduction

Harmane, harmine and norharmane are β-carboline compounds that have been found in a number of medicinal plants, tobacco smoke, well-cooked foods (Poindexter and Carpenter, 1962; Nishigata et al., 1980; Herraiz, 2000) and in mammalian tissues (Airaksinen and Kari, 1981; Guan et al., 2001; Anderson et al., 2006). β-carboline compounds act as inverse agonists at the benzodiazepine site of the γ-aminobutyric acid type A ($GABA_A$) receptors and have actions diametrically opposite to those of the anxiolytic benzodiazepines (Rommelspacher et al., 1981; Prado de Carvalho et al., 1983; Allen et al., 1992; Chapouthier and Venault, 2003). These compounds are also associated with the potentiation of monoaminergic pathways through monoamine oxidase (MAO) A or B inhibition (Kim et al., 1997; Rommelspacher et al., 2002; Herraiz and Chaparro, 2005; Herraiz et al., 2010), blockade of reuptake sites and direct activation of monoamine receptors (Komulainen et al., 1980; Sällström-Baum et al., 1995, 1996; Tella, 1995; Glennon et al., 2000). Neurochemical and behavioral studies have shown that some β-carbolines facilitate the dopaminergic transmission (Pimpinella and Palmery, 1995) and interact with D_1 and D_2 dopaminergic receptors (Müller et al., 1981; Pawlik and Rommelspacher, 1988; Nasehi et al., 2010) in the striatum, a structure known to be involved in stereotyped licking behavior (Costall et al., 1972; Ungerstedt, 1979; Zarrindast et al., 1992). The stereotyped licking behavior is thought to be produced by activation of both postsynaptic dopamine D_1 and D_2 receptors (Ungerstedt, 1979; Zarrindast et al., 1992). In this respect, a $GABA_A$ mechanism in the striatum has also been identified. Stereotypy produced by peripheral or central injection of direct- or indirect-acting dopaminergic agents is blocked by intrastriatal injection of $GABA_A$ antagonists. Moreover, intrastriatal $GABA_A$ agonists induce stereotyped behavior which is indistinguishable from that produced by apomorphine or amphetamine (Childs and Gale, 1983; Karler et al., 1995). These data suggest that a GABAergic process in the striatum is involved in the neuroeffector mechanisms mediating the stereotypy evoked by dopaminergic agents. It is reasonable, therefore, to propose that β-carboline inverse agonists at the benzodiazepine/$GABA_A$ receptor complex may modulate this striatal mechanism. The present study was carried out to examine the effects of the β-carbolines harmane, harmine and norharmane on the stereotyped licking behavior induced by the mixed dopamine D_1/D_2 receptor agonist, apomorphine in rats.

2. Materials and methods

2.1. Animals

All experiments were carried out on male Wistar albino rats from the Pasteur Institute (Iran), 200–250 g in body weight. The animals were housed 5 per plastic cage in an animal room maintained at 21 ± 2 °C on a 12-h light/dark cycle (lights on at 0700–1900 h). Standard laboratory rat chow (Pars, Iran) and water were available at all times except during the experiments. Each animal was used once only.

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2.2. Licking measurement

For the apomorphine-induced licking test, animals were observed in a clear, cylindrical chamber (25 cm wide and 25 cm high) for a 75-min period according to previous reports (Zarrindast et al., 1992; Farzin and Attarzadeh, 2000). A mirror was arranged in an oblique position under the cylinder to make recording of licking possible. Animals were allowed 30 min to accommodate prior testing. Immediately after apomorphine injection (0.5 mg/kg, s.c.), the animals were placed singly into the cylinder and the number of licks (protrusion of the tongue against the cylinder wall or floor) were recorded by a direct observer during a 75-min period. The observer was blind to treatment. The experimental protocol was approved by the Research and Ethics Committee of Mazandaran University of Medical Sciences.

2.3. Drugs

The following drugs were used: R(-)-apomorphine HCl (Research Biochemicals, USA), flumazenil (Sigma, USA), harmane HCl (Sigma, USA), harmine HCl (Sigma, USA), norharmane HCl (Sigma, USA) and reserpine (Sigma, USA). The drugs were dissolved in saline, except for reserpine and flumazenil, which were dissolved in a drop of acetic acid and then diluted with saline. In these cases, the vehicle control was acetic acid in saline. Reserpine (5 mg/kg, i.p.) was injected to animals around 18 h before test to deplete of the striatal dopamine content (Zarrindast and Minaian, 1991; LaBuda and Fuchs, 2002). It is well known that reserpine (5 mg/kg, 17 to 19 h before testing) produce a marked reduction in the dopamine concentration of the rat striatum (Guldberg and Broch, 1971). Drug concentrations were prepared so that the necessary dose could be injected in a volume of 1 ml/kg by i.p. or s.c. route. The doses of drugs and pretreatment time were usually those used previously and shown to be pharmacologically active (Pimpinella and Palmery, 1995; Sällström-Baum et al., 1996; Farzin and Attarzadeh, 2000; Nasehi et al., 2010).

2.4. Statistical analysis

One-way analysis of variance (ANOVA) followed by the Newman–Keuls multiple comparisons test was used for statistical analysis. Differences with $P<0.05$ between the experimental groups at each point were considered statistically significant. All data were analyzed with the computer program, GraphPad Prism Software (V5).

3. Results

3.1. Effects of harmane, norharmane and harmine on apomorphine-induced liking behavior

Subcutaneous injection of apomorphine (0.5 mg/kg) to rats induced licking. The licking response was reduced in animals pretreated with harmane (1.25–5 mg/kg, i.p.) [$F(3, 27)=4.87$, $P<0.0078$, n = 7–10 rats/group, and $ED_{50}=4$ mg/kg], norharmane (1.25–5 mg/kg, i.p.) [$F(3, 29)=20.22$, $P<0.0001$, n = 7–10 rats/group, and $ED_{50}=2.5$ mg/kg] and harmine (2.5–10 mg/kg, i.p.) [$F(3, 29)=4.068$, $P<0.0158$, n = 7–10 rats/group, and $ED_{50}=7.8$ mg/kg], 20 min before apomorphine (the ED_{50} value obtained by regression analysis) (Fig. 1).

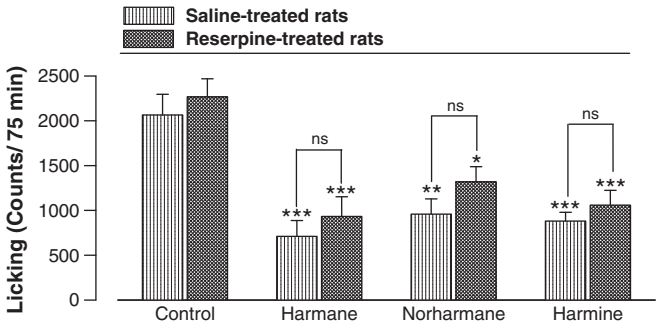

Fig. 2. Effects of harmane, norharmane and harmine on the licking behavior in reserpine-pretreated rats. Harmane (4 mg/kg, i.p.), norharmane (2.5 mg/kg, i.p.) and harmine (7.8 mg/kg, i.p.) were injected in animals pretreated with saline (1 ml/kg, i.p.) or reserpine (5 mg/kg, i.p., 18 h before the test), 20 min before apomorphine (0.5 mg/kg, s.c.). Results are expressed as means ± S.E.M. (n = 7–10 rats/group). *P<0.05, **P<0.01, and ***P<0.001, different from the control group.

3.2. Effects of harmane, norharmane and harmine on the liking behavior in reserpine pretreated rats

In rats pretreated with reserpine (5 mg/kg, i.p., 18 h before the test), the inhibitory effects of harmane (4 mg/kg, i.p) [$F(3, 25)=13.799$, $P<0.0001$, and n = 7–8 rats/group], norharmane (2.5 mg/kg, i.p.) [$F(3, 25)=9.569$, $P<0.0002$, and n = 7–8 rats/group] and harmine (7.8 mg/kg, i.p.) [$F(3, 25)=14.002$, $P<0.0001$, and n = 7–8 rats/group] were unchanged (Fig. 2).

3.3. Effects of harmane, norharmane and harmine on the liking behavior in flumazenil treated rats

In rats treated with different doses of flumazenil i.p., 20 min before apomorphine (0.5 mg/kg, s.c.), a low dose of 2 mg/kg flumazenil was ineffective in reducing the licking behavior, while higher doses of the drug (4 and 8 mg/kg) were effective [$F(3, 25)=6.344$, $p<0.0024$, and n = 7–8 rats/group] (Fig. 3). The dose of 2 mg/kg flumazenil i.p., which was ineffective in modifying the licking response, significantly antagonized the inhibitory effects of harmane (4 mg/kg) [$F(3, 25)=5.618$, $P<0.0044$, and n = 7–8 rats/group], norharmane (2.5 mg/kg) [$F(3, 25)=6.240$, $p<0.0026$, and n = 7–8 rats/group] and harmine (7.8 mg/kg) [$F(3, 25)=7.342$, $P<0.0011$, and n = 7–8 rats/group] (Fig. 4).

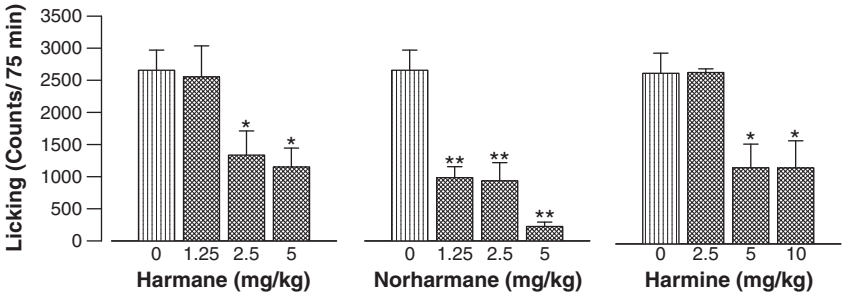

Fig. 1. Effects of harmane, norharmane and harmine on apomorphine-induced licking behavior in rats. All agents were injected i.p. 20 min before apomorphine (0.5 mg/kg, s.c.). Results are expressed as means ± S.E.M. (n = 7–10 rats/group). *P<0.05 and **P<0.001, different from the control group.

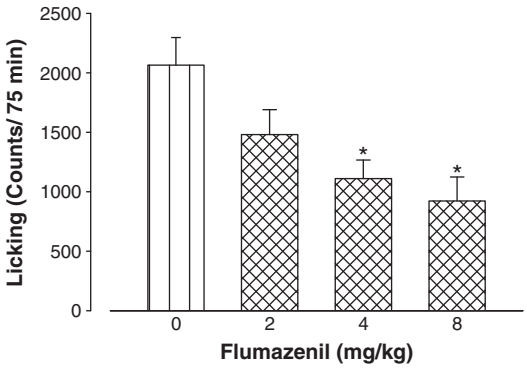

Fig. 3. Effect of flumazenil on apomorphine-induced licking behavior in rats. Flumazenil was injected i.p. 20 min before apomorphine (0.5 mg/kg, s.c.). Results are expressed as means ± S.E.M. (n = 7–8 rats/group). *P<0.01, different from the control group.

4. Discussion

In the present study, the effects of harmane, harmine and norharmane on apomorphine-induced licking behavior in rat were examined. The main findings are as follows.

(a) Harmane, harmine and norharmane were remarkably effective in reducing apomorphine-induced licking behavior.
(b) The inhibitory effects of these compounds were prevented in rats treated by flumazenil but not by reserpine.

These findings have been in part confirmed in several studies, showing that apomorphine-induced licking behavior can be suppressed by harmane and related β-carbolines (Kari et al., 1980; Müller et al., 1981). The attenuating effects of harmane, harmine and norharmane on the licking behavior may be explained by several mechanisms.

One possible mechanism may be an interaction with benzodiazepine receptors in an inverse manner. Harmane, harmine and norharmane are present in the brain (Airaksinen and Kari, 1981; Beck and Faull, 1986; Moncrieff, 1989). The origin of these β-carbolines in the brain may be exogenous, e.g. after consuming various foodstuffs or smoking tobacco (Poindexter and Carpenter, 1962; Nishigata et al., 1980; Herraiz, 2000; Rommelspacher et al., 2002) and/or endogenous, i.e. after reaction of tryptamine with acetaldehyde or with pyruvic acid (Schouten and Bruinvels, 1986; Moncrieff, 1989; Rommelspacher et al., 1991). These β-carbolines bind to benzodiazepine site of the $GABA_A$ receptors as inverse agonists (Rommelspacher et al., 1981; Prado de Carvalho et al., 1983; Allen et al., 1992; Chapouthier and Venault, 2003). Both electrophysiological and behavioral effects of β-carbolines as well as benzodiazepines are antagonized by flumazenil (Hoffman and Warren, 1993). In the present study, flumazenil at a dose ineffective *per se* (2 mg/kg, i.p.) on the licking response, antagonized the effects of the β-carbolines. Our findings provide evidence for an inverse agonistic mechanism located in the benzodiazepine receptors. According to the present findings, the rank order of potency of the β-carbolines in reducing the licking behavior was norharmane > harmane > harmine. In agreement with our data, it has been shown that norharmane, the most potent compound, displaced [^{3}H]flunitrazepam from the benzodiazepine binding site with an IC_{50} 6 μM, whereas harmane and harmine were less potent than norharmane with IC_{50}s 25 μM and 200 μM, respectively (Robertson et al., 1981). These results add further data to support an involvement of benzodiazepine site in reducing the licking behavior. For flumazenil, it is interesting to note that both doses of 4 and 8 mg/kg were effective in reducing apomorphine-induced licking behavior. It is very well known that flumazenil acts predominantly as a specific antagonist at benzodiazepine receptors (Bonetti et al., 1982; File and Cooper, 1985), although it may act as an inverse agonist after relatively high doses (File and Pellow, 1985). Since the β-carboline inverse agonists used in the present experiment reduced the licking response, it may be that the higher doses of flumazenil suppress the licking behavior by such a mechanism. However, further work is necessary to investigate the dose–response relationships between the dose of flumazenil and its effects on apomorphine-induced licking behavior.

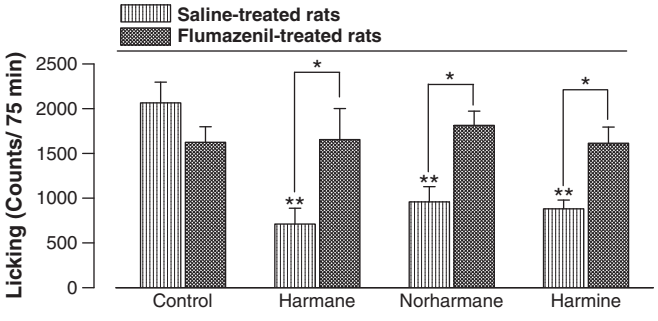

Fig. 4. The effects of harmane, norharmane and harmine alone or in combination with flumazenil. Harmane (4 mg/kg, i.p.), norharmane (2.5 mg/kg, i.p.), harmine (7.8 mg/kg, i.p.), flumazenil (2 mg/kg, i.p.) and saline (1 ml/kg, i.p.) were injected to rats 20 min before apomorphine (0.5 mg/kg, s.c.). Results are expressed as means ± S.E.M. (n = 7–8 rats/group). *P<0.05 and **P <0.01, different from the control group.

Another possibility for the inhibitory effects of the β-carbolines on the licking behavior may be an interaction with dopaminergic system. At this point it should be noted that harmane and other β-carbolines interact with monoaminergic pathways through inhibition of monoamine oxidase A or B (Kim et al., 1997; Rommelspacher et al., 2002; Herraiz and Chaparro, 2005; Herraiz et al., 2010) and monoamine reuptake systems (Komulainen et al., 1980; Sällström-Baum et al., 1995, 1996; Tella, 1995; Glennon et al., 2000). Most of the investigations conducted to ascertain the dopaminergic actions of β-carbolines have reported that these compounds have antidopaminergic activity (Westermann et al., 1976; Kari et al., 1980; Müller et al., 1981; Matsubara et al., 1998). In this respect, Tam and Roth (1985) have also reported a decrease in dopamine metabolism in the rat striatum after an anxiogenic β-carboline, N-methyl-β-carboline-3-carboxamide (FG 7142) treatment, suggesting an inhibition of the nigrostriatal dopamine system by this β-carboline. This suggestion is further supported by the observation that β-carbolines increase the firing rate of zona reticulata (ZR) cells in the substantia nigra (Mereu et al., 1983). An activation of the ZR cells could result in an inhibition of dopamine cells in the zona compacta that project to the striatum, and thus reduce dopamine transmission in the striatum (Grace and Bunney, 1979). There are several studies indicating that the activating effect of harmane and other β-carbolines on dopamine efflux is dose-dependent, U shaped, with low doses (μg range, i.p. injections) of compounds activating dopamine efflux and high doses (mg range, i.p. injections) inhibiting it (Ergene and Schoener, 1993; Sällström-Baum et al., 1995, 1996). The doses used in the present experiments is in the high dose category, therefore we can reasonably speculate that the effects of the β-carboline compounds used in the present experiments are likely unrelated to an activating effect on dopamine efflux. Our findings are in agreement with this hypothesis, because the pretreatment of animals with reserpine did not modify the effects of harmane, norharmane and harmine. The effect can be explained by an inhibition of postsynaptic dopaminergic transmission which is modulated by an action on the benzodiazepine/$GABA_A$ receptor complex, because flumazenil abolished the β-carboline-induced decrease in the licking behavior. It is noteworthy that the benzodiazepinergic system interacts functionally with the dopamine transmission in various brain regions. For example, a basal dopaminergic tonus, by stimulating both dopamine D_1 and D_2 receptors, induces an anxious-like state that is suppressed by the benzodiazepine anxiolytic diazepam (Geller, 1964). Previous studies have also shown that dopamine receptor stimulation in the striatum activates the descending striato-entopeduncular, striato-nigral and pallido-subthalamic GABA

pathways and consequently induces a GABA mediated inhibition of efferent neurons localized in these nuclei (Scheel-Kriiger et al., 1980; Westerling et al., 1989). Local injection of GABA agonists into these nuclei caused a behavioral syndrome very similar to what was observed after peripheral injections of apomorphine or amphetamine (Scheel-Kriiger et al., 1980). Thus, benzodiazepine/GABA mechanisms might influence dopamine mediated behavior. However, at this moment it is still unclear whether dopamine- or benzodiazepine/GABAergic component contributes most to the observed decrease of the licking behavior. Further experiments should be undertaken to elucidate the putative participation of these systems on the licking behavior.

It has also been reported that an interacting antagonism between dopaminergic and serotoninergic systems exist in the brain, with serotoninergic projections inhibiting dopaminergic function at several levels (Kapur and Remington, 1996; Sällström-Baum et al., 1996). Since β-carbolines facilitate serotoninergic transmission (Sällström-Baum et al., 1996) and pretreatment with 5-hydroxy-tryptophan antagonizes dopaminergic stereotyped behaviors (Weiner et al., 1973), it therefore seems likely that the β-carbolines harmane, harmine and norharmane reduce the licking behavior by such a mechanism. However, the effects on the licking behavior of the β-carbolines tested in reserpine-treated rats do not support the idea of an involving serotoninergic mechanism.

In conclusion, the present study demonstrates that the β-carbolines harmane, harmine and norharmane inhibit apomorphine-induced licking behavior in rat. This effect seems to be not mediated by presynaptic monoaminergic mechanisms, but appears to be induced by an inverse-agonistic mechanism located in the benzodiazepine receptors. Further experiments are needed to determine the precise mechanisms by which the β-carbolines harmane, harmine and norharmane alter the licking behavior.

Acknowledgements

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