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Pharmacological Properties of β-Amyrin Palmitate, a Novel Centrally Acting Compound, Isolated from *Lobelia inflata* Leaves

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Abstract—Effects of β-amyrin palmitate isolated from the leaves of *Lobelia inflata* were studied on the central nervous system of mice and were compared with those of antidepressant drugs, mianserin and imipramine. In the forced swimming test, β-amyrin palmitate, like mianserin and imipramine, reduced the duration of immobility of mice significantly in a dose-dependent manner (5, 10 and 20 mg kg^{-1}). β-Amyrin palmitate (5, 10 and 20 mg kg^{-1}) or mianserin (5, 10 and 20 mg kg^{-1}) elicited a dose-related reduction in locomotor activity of mice and antagonized locomotor stimulation induced by methamphetamine. In contrast, imipramine (5, 10 and 20 mg kg^{-1}) increased locomotor activity and potentiated methamphetamine-induced hyperactivity. β-Amyrin palmitate showed no effect on reserpine-induced hypothermia, whilst mianserin (10 mg kg^{-1}) and imipramine (10 and 20 mg kg^{-1}) antagonized the reserpine-induced effect. Unlike imipramine, β-amyrin palmitate and mianserin did not affect haloperidol-induced catalepsy, tetrabenazine-induced ptosis and apomorphine-induced stereotypy. β-Amyrin palmitate and imipramine had no effects on the head-twitch response induced by 5-hydroxytryptophan, whereas mianserin (5, 10 and 20 mg kg^{-1}) decreased it in a dose-dependent manner. A potentiating effect of β-amyrin palmitate (5, 10 and 20 mg kg^{-1}) on narcosis induced by sodium pentobarbitone was stronger than that of imipramine (10, 20 and 40 mg kg^{-1}) but weaker than that of mianserin (2·5, 5 and 10 mg kg^{-1}). These results suggest that β-amyrin palmitate has similar properties in some respects to mianserin and might possess a sedative action. We suggest that β-amyrin palmitate has antidepressant activity with a mianserin-like profile of action.

The leaves of *Lobelia inflata* L. (Campanulaceae), which have been used as a remedy for spasmodic asthma (Henry 1924), reportedly contain many alkaloids with piperidine skeletons (Marion 1950). Among the lobelia alkaloids, lobeline is the most important with pharmacological activity in the central nervous system (Henry 1924; Barlow & Franks 1971) and the cardiovascular system (Korczyn et al 1969).

Our studies on naturally occurring active compounds have been focused on those possessing potential antidepressant activity, as a discovery of new types of antidepressants would be clinically beneficial. In our recent work on the leaves of *L. inflata*, we have successfully isolated β-amyrin palmitate which showed antidepressant activity in the forced swimming test in mice. A preliminary account of some of the findings has been presented elsewhere (Subarnas et al 1992). The discovery of the antidepressant activity of β-amyrin palmitate has stimulated us to evaluate the detailed pharmacological effects of this compound in the central nervous system. In the present study, we used mianserin and imipramine as reference compounds because they are clinically used as antidepressants with different structures and different mechanisms of action.

Materials and Methods

Animals

Male ddy strain mice, 23–27 g, were placed in plastic cages with free access to food and water, and housed under standard conditions (room temperature: 23 ± 1°C; constant humidity). The room light was automatically controlled on a 12 h light/dark cycle. All experiments were carried out in the room in which the mice were housed.

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Forced swimming test

Measurement of immobility in mice was carried out according to a modified method of Porsolt et al (1978). Mice were individually placed for 5 min in vertical glass cylinders (height 20 cm; diam. 10 cm) containing 8 cm of water maintained at 25°C. They were removed and allowed to dry in a drying room. On the next day, 1 h after an intraperitoneal injection of the compounds, they were replaced in the glass cylinders, and the total duration of immobility was measured during a 5 min test. The mice were judged to be immobile whenever they remained floating passively in the water in a slightly hunched but upright position with their head above the surface.

Locomotor activity

Locomotor activity was measured by Animex Auto MK-110. Mice were individually placed in the activity cages and the cages were put on Animex activity meters. The mice were allowed 15 min to adapt. In the experiment of single administration of the test compounds, mice were injected intraperitoneally with vehicle (Tween 80, 0·5%) or the test compounds, and the activity of mice was measured immediately after the injection. The number of the activity counts was recorded every 15 min in a 90 min period. In the experiment in which the test compounds were combined with methamphetamine (1 mg kg^{-1}), the mice were firstly given vehicle or the test compounds, and 30 min later methamphetamine was administered. The activity of mice was measured immediately after the administration of methamphetamine.

The number of the activity counts was recorded every 15 min in a 90 min period. The experiments were carried out from 0900 to 1600 h.

Reserpine-induced hypothermia

Before the test, rectal temperature of all mice was measured by a thermoelectric probe inserted into the rectum with a contact depth of 2 cm. Groups of ten mice with the rectal temperature of 37·0–38·0°C were selected for the test. The mice were individually treated with reserpine (2 mg kg^{-1}) subcutaneously and placed in plastic cages with enough food and water and maintained in the temperature-controlled room (23°C). Eighteen hours after treatment with reserpine, the mice were given vehicle (Tween 80, 0·5%) or the test compounds intraperitoneally. The rectal temperature of mice was measured 15 min after the administration of vehicle or the test compounds and subsequently measured every 15 min for 2 h.

Haloperidol-induced catalepsy

Haloperidol (5 mg kg^{-1}, i.p.) was given to mice 30 min after an intraperitoneal administration of vehicle (Tween 80, 0·5%) or the test compounds. Mice were tested for catalepsy according to the modified method of Costall & Olley (1971). Intensity of catalepsy, measured as the time the mice remained with both front paws extending over a bar, was converted to a numerical score. Score 0: 0–4 s; score 1: 5–9 s; score 2: 10–14 s; score 3: 15–19 s; score 4: 20–24 s; score 5: over 25 s. The test for the presence or the absence of catalepsy was started 30 min after the administration of haloperidol and continued every 30 min for 2 h. The mice were classed as cataleptic if they retained the abnormal positions for 20 s or more. Catalepsy was observed by one of the authors who was unaware of which drugs were used in the treatment. Ten mice were used for each treatment.

Tetrabenazine-induced ptosis

Mice were injected with tetrabenazine (50 mg kg^{-1}, i.p.) 30 min after the administration of vehicle (Tween 80, 0·5%) or the test compounds and individually placed in plastic cages. The observation of ptosis was begun 30 min after the injection of tetrabenazine and continued in 30 min intervals for 2 h. The test for ptosis was carried out based on the method of Janssen et al (1956). In this test, a scoring system was used to express the degree of palpebral ptosis in mice. Score 0: eyes completely closed; score 2: half-open eyes; score 4: wide-open eyes; score 1 and 3: intermediate value. Ptosis was observed by one of the authors who was unaware of which drugs were used in the treatment. Ten mice were used for each treatment.

Apomorphine-induced stereotyped behaviours

Mice were treated intraperitoneally with vehicle (Tween 80, 0·5%) or the test compounds, and were injected with apomorphine (10 mg kg^{-1}, s.c.) 30 min later. The mice were placed in individual plastic cages (25 × 18 × 13 cm) immediately. Duration of stereotypy such as licking was measured for 2 min at 10 min intervals from 10 to 90 min after the mice received apomorphine. The stereotypy was measured by one of the authors who was unaware of which drugs were used in the test. Ten mice were used for each treatment.

5-Hydroxytryptophan-induced head-twitch response

Mice were pretreated with a monoamine oxidase (MAO) inhibitor, clorgyline (1 mg kg^{-1}, i.p.), and given vehicle (Tween 80, 0·5%) or the test compound intraperitoneally 30 min after pretreatment with clorgyline. 5-Hydroxytryptophan (5-HTP) (150 mg kg^{-1}, i.p.) was administered to the mice 30 min after the injection of vehicle or the test compounds. The mice were individually placed in plastic cages (25 × 18 × 13 cm) immediately after the administration of 5-HTP. The number of head-twitches was counted for 2 min at 10 min intervals from 10 to 90 min after the administration of 5-HTP, and the total number was counted for 90 min. These numbers were counted by one of the authors who was unaware of which drugs were used in the test. Ten mice were used for each treatment.

Pentobarbitone-potentiated narcosis

Mice were injected with sodium pentobarbitone (50 mg kg^{-1}, i.p.) 30 min after pretreatment with vehicle (Tween 80, 0·5%) or the test compounds. The mean duration of sleep of mice was compared between that of mice injected with sodium pentobarbitone after pretreatment with vehicle and that of mice administered sodium pentobarbitone after pretreatment with the test compounds. The criterion for sleep was indicated by the loss of the righting reflex.

Drugs

Drugs or compounds used in this study are as follows. β-Amyrin palmitate (isolated from the leaves of *Lobelia inflata* in our laboratory), mianserin hydrochloride (Sigma Chemical Company Ltd, USA), imipramine hydrochloride (Ciba Geigy Pharmaceutical Company Ltd, Japan), methamphetamine (Dainhon Company Ltd, Japan), reserpine (Nakarai Chemicals Ltd, Japan), haloperidol (Wako Pure Chemical Company), tetrabenazine (ICN Pharmaceuticals Inc, USA), apomorphine hydrochloride (Sigma Chemical Company, Ltd, USA), 5-hydroxy-L-tryptophan (Nakarai Chemicals Ltd, Japan), clorgyline hydrochloride (May & Baker Ltd, UK), sodium pentobarbitone (Tokyo Kasei Company Ltd, Japan), ascorbic acid (Wako Pure Chemical Industries, Ltd, Japan).

β-Amyrin palmitate, reserpine, haloperidol, tetrabenazine and 5-hydroxy-L-tryptophan with added ascorbic acid (0·1%) were dispersed in a suspension of Tween 80 (0·5% w/v 0·9% NaCl). Mianserin hydrochloride, imipramine hydrochloride, methamphetamine, apomorphine hydrochloride, clorgyline hydrochloride, sodium pentobarbitone and ascorbic acid were dissolved in saline.

Statistical analysis

Data were analysed by analysis of variance, and the significance of difference was calculated according to Dunnett's test.

Results

Effects of β-amyrin palmitate, mianserin and imipramine on the duration of immobility

The three compounds, β-amyrin palmitate, mianserin and imipramine, all at doses of 5, 10 and 20 mg kg^{-1}, exhibited a dose-dependent reduction in the duration of immobility of

Table 1. Effects of β-amyrin palmitate, mianserin and imipramine on the duration of immobility.

Drug	Dose (mg kg^{-1})[1]	Duration of immobility (% control ± s.e.)
Tween 80	—	100
β-Amyrin palmitate	5	78·0 ± 4·0*
	10	67·4 ± 6·4**
	20	62·4 ± 7·4**
Mianserin	5	92·5 ± 6·7
	10	81·3 ± 4·3**
	20	53·6 ± 5·7**
Imipramine	5	76·7 ± 9·3
	10	64·5 ± 6·1**
	20	54·4 ± 9·4**

[1] Ten mice per dose. The duration of immobility was measured for 5 min. *$P < 0.05$; **$P < 0.01$ compared with the control values.

mice in the forced swimming test (Table 1). β-Amyrin palmitate reduced the duration of immobility significantly at the three doses used, whereas mianserin and imipramine showed a significant effect only at doses of 10 and 20 mg kg^{-1}.

Effects of β-amyrin palmitate, mianserin and imipramine on locomotor activity

Single administration. As shown in Fig. 1, β-amyrin palmitate or mianserin elicited a dose-dependent reduction in locomotor activity of mice. β-Amyrin palmitate at doses of 10 and 20 mg kg^{-1} reduced locomotor activity significantly 15–60 min after the administration of β-amyrin palmitate to mice. Mianserin at a dose of 5 mg kg^{-1} produced significant reduction in locomotor activity in the first 30 min, and the increasing doses to 10 and 20 mg kg^{-1} decreased the activity from 15 to 45 min and 15 to 60 min, respectively, after the injection of mice with mianserin. In contrast, imipramine enhanced locomotor activity of mice, but the enhancement was decreased with the increasing doses. The significantly increased locomotion was produced by a dose of 5 mg kg^{-1} from 60 to 90 min after the administration of imipramine. A significant decrease in locomotion was elicited by a dose of 20 mg kg^{-1} of imipramine in the first 30 min.

In combination with methamphetamine. Effects of β-amyrin palmitate, mianserin and imipramine on locomotor stimulation induced by methamphetamine (1 mg kg^{-1}) are shown in Fig. 2. Methamphetamine given to mice pretreated with vehicle increased locomotor activity significantly as compared with that produced by vehicle alone. This methamphetamine-induced stimulation was antagonized by β-amyrin palmitate or mianserin, but was potentiated by imipramine. Pretreatment of mice with β-amyrin palmitate at doses of 10 and 20 mg kg^{-1} elicited a significant reduction in methamphetamine-induced stimulation 15 min after the administration of methamphetamine, and the reduction disappeared after 75 min. Pretreatment with mianserin at a dose of 10 mg kg^{-1} markedly reduced stimulation produced by methamphetamine from 15 to 75 min after the administration of methamphetamine, and at a dose of 20 mg kg^{-1}, decreased locomotor stimulation significantly during a 90 min test period. In contrast, imipramine potentiated methamphetamine-induced stimulation in a dose-dependent manner.

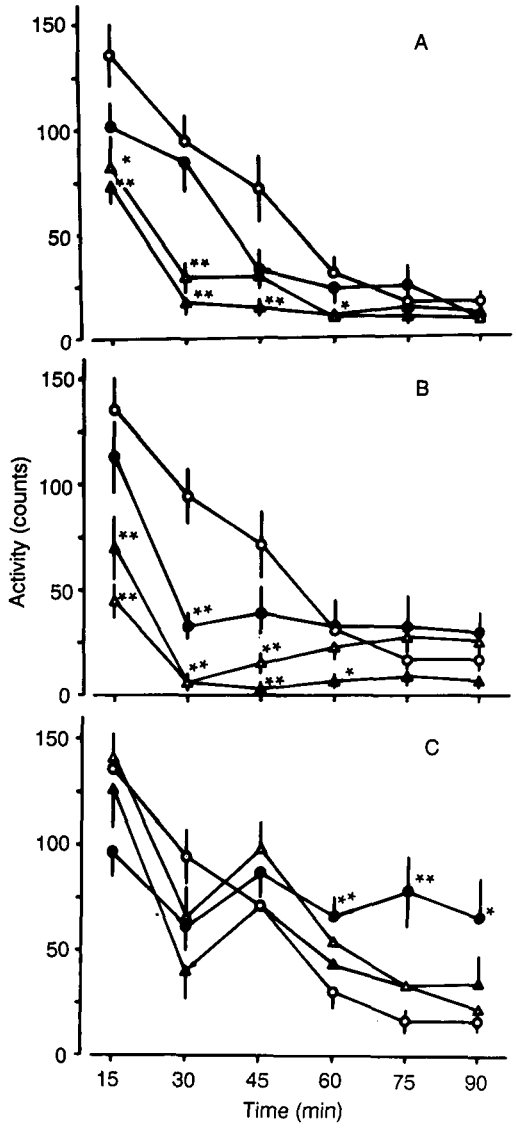

FIG. 1. Effects of β-amyrin palmitate (A), mianserin (B) and imipramine (C) on locomotor activity of mice. Each point indicates the mean value of activity counts. ○ Vehicle, ● 5, △ 10, ▲ 20 mg kg^{-1}. Vertical bars represent standard errors of means (s.e.m.). *$P < 0.05$, **$P < 0.01$ compared with the control values. Ten mice were used for each dose.

Effects of β-amyrin palmitate, mianserin and imipramine on reserpine-induced hypothermia

Rectal temperature of reserpine-treated mice fell to 27–29°C, 18 h after the mice were treated with reserpine (2 mg kg^{-1}). β-Amyrin palmitate, at doses of 10 and 20 mg kg^{-1}, administered to the reserpine-pretreated mice did not affect the rectal temperature. Mianserin, at a dose of 10 mg kg^{-1}, antagonized hypothermia induced by reserpine. Imipramine, at doses of 10 and 20 mg kg^{-1}, produced a significant rise in reserpine-induced hypothermia in a dose-dependent manner (control, 31·3°C; β-amyrin palmitate, 10 mg kg^{-1} 31·0°C and 20 mg kg^{-1} 32·1°C; mianserin, 10 mg kg^{-1} 34·1°C and 20 mg

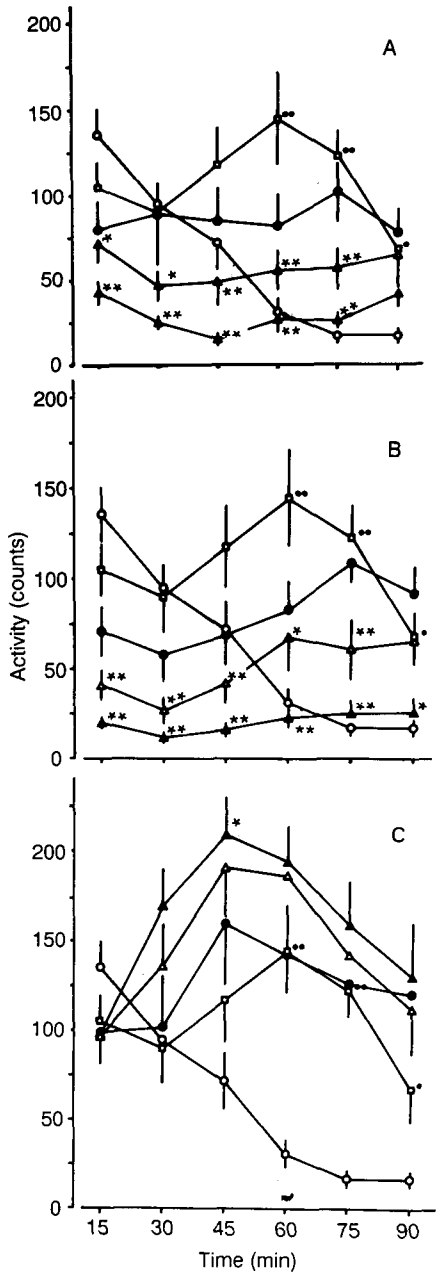

FIG. 2. Effects of β-amyrin palmitate (A), mianserin (B) and imipramine (C) on methamphetamine-induced locomotor stimulation of mice. Each point indicates the mean value of activity counts. ○ Vehicle, □ vehicle + methamphetamine, ● 5, △ 10, ▲ 20 mg kg^{-1}. Vertical bars represent standard errors of means (s.e.m.) $*P<0.05$, $**P<0.01$ compared with the vehicle + methamphetamine values. $\bullet P<0.05$, $\bullet\bullet P<0.01$ compared with the vehicle values. Ten mice were used for each dose.

kg^{-1} 30·4°C; imipramine, 10 mg kg^{-1} 34·8°C and 20 mg kg^{-1} 35·1°C). β-Amyrin palmitate itself did not alter the rectal temperature of mice at a dose of 20 mg kg^{-1} (control 37·5°C; β-amyrin palmitate 36·8°C).

Effects of β-amyrin palmitate, mianserin and imipramine on haloperidol-induced catalepsy

Haloperidol (5 mg kg^{-1}) induced catalepsy in mice pretreated with vehicle. The cataleptic effect induced by haloperidol was not affected by β-amyrin palmitate or mianserin, but reduced by imipramine at a dose of 20 mg kg^{-1} (control score 5·0; β-amyrin palmitate, 20 mg kg^{-1} score 4·7; mianserin, 20 mg kg^{-1} score 4·9; imipramine, 20 mg kg^{-1} score 2·8).

Table 2. Effects of β-amyrin palmitate, mianserin and imipramine on sodium pentobarbitone-induced narcosis in mice.

Drug	Dose (mg kg^{-1})[1]	Potentiation Mean ± s.e. (s)	Potentiation Increase (%)
Tween 80	—	45 ± 5	0
β-Amyrin palmitate	5	73 ± 3**	62
	10	86 ± 6**	91
	20	84 ± 8**	87
Mianserin	2·5	72 ± 9**	60
	5	101 ± 9**	124
	10	110 ± 6**	144
Imipramine	10	49 ± 7	9
	20	92 ± 5**	104
	40	115 ± 11**	156

[1] Ten mice per dose. Vehicle or the test compounds were given to mice 30 min before the administration of sodium pentobarbitone (50 mg kg^{-1}). $**P<0.01$ compared with the control values.

Effects of β-amyrin palmitate, mianserin and imipramine on tetrabenazine-induced ptosis

Tetrabenazine (50 mg kg^{-1}) administered to mice pretreated with vehicle induced ptosis. β-Amyrin palmitate or mianserin at doses of 10 and 20 mg kg^{-1} did not affect tetrabenazine-induced ptosis, whereas imipramine at the same doses showed a dose-related antagonistic effect (control score 0·6; β-amyrin palmitate, 10 mg kg^{-1} score 0·1 and 20 mg kg^{-1} score 0·5; mianserin, 10 mg kg^{-1} score 0·4 and 20 mg kg^{-1} score 0·6; imipramine, 10 mg kg^{-1} score 2·4 and 20 mg kg^{-1} score 3·7).

Effects of β-amyrin palmitate, mianserin and imipramine on apomorphine-induced stereotypy

In mice, apomorphine given alone at a dose of 10 mg kg^{-1} induced stereotyped behaviours such as sniffing, increased locomotion, rearing and licking. β-Amyrin palmitate and mianserin at doses of 10 and 20 mg kg^{-1} did not affect the duration of licking induced by apomorphine, but imipramine at the same doses potentiated the duration of licking significantly (control 360 s; β-amyrin palmitate, 10 mg kg^{-1} 422 s and 20 mg kg^{-1} 282 s; mianserin, 20 mg kg^{-1} 435 s; imipramine, 10 mg kg^{-1} 508 s and 20 mg kg^{-1} 682 s).

Effects of β-amyrin palmitate, mianserin and imipramine on 5-HTP-induced head-twitch response

5-HTP (150 mg kg^{-1}) elicited head-twitch response in mice pretreated with clorgyline (1 mg kg^{-1}) and vehicle successively. β-Amyrin palmitate or imipramine at doses of 10 and 20 mg kg^{-1} given to mice after the administration of clorgyline showed no effects on the head-twitch response produced by 5-HTP, whereas mianserin at the same doses significantly decreased the number of 5-HTP-induced head-twitches (control 105·0; β-amyrin palmitate, 10 mg kg^{-1} 80·4 and 20 mg kg^{-1} 83·3; mianserin, 10 mg kg^{-1} 44·7 and 20 mg kg^{-1} 21·7; imipramine, 10 mg kg^{-1} 109·0 and 20 mg kg^{-1} 77·0).

Effects of β-amyrin palmitate, mianserin and imipramine on pentobarbitone-induced narcosis

As shown in Table 2, β-amyrin palmitate at doses of 5, 10 and 20 mg kg^{-1} potentiated pentobarbitone-induced narcosis in mice significantly. However, the potentiation was not dependent on the dose since the effect of 20 mg kg^{-1} was slightly weaker than that of 10 mg kg^{-1}. Mianserin at doses of 2·5, 5 and 10 mg kg^{-1} significantly prolonged the pentobarbitone-induced sleeping time in a dose-dependent manner. On the other hand, imipramine potentiated the pentobarbitone narcosis at higher doses, 20 and 40 mg kg^{-1}.

Discussion

In our preliminary study, we examined the antidepressant activity of β-amyrin palmitate using the forced swimming test. This method, as reported by Porsolt et al (1977a, b, 1978), is selectively sensitive to clinically effective antidepressant drugs and non-pharmacological antidepressant treatments such as electroconvulsive shock and REM sleep deprivation. They suggested that this method may be capable of discovering new antidepressants not readily identified by classical screening tests, because atypical antidepressants such as iprindol and mianserin, which are undetectable in classical tests, show positive results in the forced swimming test. In the swimming test, β-amyrin palmitate, like mianserin and imipramine, decreased the duration of immobility of mice significantly during a 5 min test, suggesting that β-amyrin palmitate might have antidepressant activity. The results of the examination of β-amyrin palmitate in the swimming test led to evaluation of pharmacological effects of β-amyrin palmitate in the central nervous system, in which some of the tests are usual tests for antidepressant drugs.

In the locomotor experiments, β-amyrin palmitate and mianserin, respectively, significantly decreased locomotor activity and antagonized methamphetamine-induced hyperactivity. It has been reported that the increase in locomotor activity induced by psychomotor stimulant drugs such as methamphetamine is mediated by both noradrenergic and dopaminergic systems, and that the stereotypy is mediated by dopaminergic systems (Andén et al 1967; Ernst 1967; Munkvad et al 1968; Roos 1969; Van Rossum 1970; Schuster 1981). Thus, the antagonism of methamphetamine-induced locomotor stimulation by β-amyrin palmitate is assumed to be due to its direct or indirect inhibitory action on noradrenergic or dopaminergic neurons. In this study, β-amyrin palmitate had no effect on apomorphine-induced stereotypy and catalepsy induced by haloperidol known as a dopamine-blocking agent. This suggests that the action of β-amyrin palmitate might not be related to a direct effect on dopaminergic systems. In the case of mianserin, Clineschmidt et al (1979) reported that mianserin decreased locomotor activity by blocking α_1-receptors because mianserin antagonizes the increases in locomotor activity produced by an α_1-agonist, phenylephrine. Furthermore, the absence of the effect of β-amyrin palmitate on stereotypy and catalepsy could also suggest that this compound is devoid of anticholinergic properties since anticholinergic drugs are known to antagonize catalepsy induced by neuroleptic drugs (Morpurgo 1962; Leslie & Maxwell 1964) and potentiate amphetamine and apomorphine-induced stereotypy (Pedersen 1967; Arnfred & Randrup 1968; Scheel-Kruger 1970). This compound showed no effect on reserpine-induced hypothermia and tetrabenazine-induced ptosis, which also suggests that β-amyrin palmitate might not have anticholinergic effects.

In the test of head-twitch response induced by 5-HTP, β-amyrin palmitate did not affect the head-twitch response indicating that this compound had no effect on 5-HT_2-receptors of 5-hydroxytryptaminergic neurons. Mianserin, known as a 5-hydroxytryptamine antagonist, caused a reduction in the number of head-twiches as was also reported by Van Riezen (1972). In conclusion, the central effects of β-amyrin palmitate were completely different from those of imipramine but were similar in some respects to those of mianserin. This compound showed sedative properties. The absence of the effects of β-amyrin palmitate in several tests classically used for screening antidepressant drugs, suggests that this compound might have antidepressant activity with mianserin-like action.

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