Characteristics of Analgesia Induced by Noncatecholic Phenylethylamine Derivatives: Possible Involvement of Endogenous Opioid Peptides and Serotonin in Phenylethylamine Analog-Induced Analgesia

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Accepted November 2, 1983

Abstract—Characteristics of the analgesic action of phenylethylamine derivatives, amphetamine, phenylethylamine (PEA), hydroxyphenylethylamine (OHPEA) and hydroxyphenylalanine (OHF), were examined. Pain threshold of mice was measured by using the hot plate method. OHPEA (50 mg/kg), amphetamine (0.5–8 mg/kg) or PEA (50 mg/kg) produced an analgesic effect in the absence of MAO inhibitor, and the analgesia was reversed by naloxone (5 mg/kg) or reserpine (2 mg/kg×2). Ten mg/kg of PEA, 250 mg/kg of OHF and 10 mg/kg of OHPEA could not produce detectable analgesia, but they revealed analgesic activity when mice were pretreated with pargyline (100 mg/kg). Analgesia induced by a combined use of PEA, OHF or OHPEA with pargyline was inhibited by naloxone or p-chlorophenylalanine (PCPA), an inhibitor of serotonin synthesis. Amphetamine-induced analgesia was also blocked by PCPA. Analgesia induced by PEA or OHPEA was blocked by methysergide (2 mg/kg). From the above findings, it was concluded that PEA, OHPEA, OHF and amphetamine possess similar characteristics in their analgesic action, and their analgesic actions involve the participation of endogenous serotonin and endogenous opioid peptides.

The existence of β-phenylethylamine (PEA) has been demonstrated in tissues and body fluids of various species of animals including human urine, blood and brain; and it has been postulated that PEA may function as a neuromodulator in the central nervous system (1). Exogenously administered PEA increases locomotor activity and induces stereotypy in rats and mice (2, 3). A high dose of PEA (100 mg/kg) produces amphetamine-like stimulation in rats (2). Giardina (4) reported that PEA and β-hydroxyphenylethylamine (OHPEA) exert an analgesic effect in pargyline-pretreated mice. Amphetamine has been well known to produce slight analgesic action (5, 6). Fischer et al. (7) suggested that many of the central nervous effects of amphetamine are closely related to endogenous PEA, and Giardina (4) reported that the analgesic activity of amphetamine may be mediated by endogenous PEA or OHPEA.

The electro-stimulation to periaqueductal gray matter (PAG) of pain patients increases enkephalin-like substance in cerebrospinal fluid (8), and the apparent analgesia in rats elicited by central gray stimulation can be attenuated at least in part by naloxone (9). Intracisternal injection of met⁵-enkephalin or leu⁵-enkephalin to mice induces analgesia (10). Injection of serotonin into the sub-arachnoid space of the pars lumbaris procures dose-dependent analgesia which can be blocked by methysergide (11). Guilbaud et al. (12) observed methysergide-reversible analgesia induced by electrostimulation to
the raphe magnus (RAM). On the basis of these findings, it is widely believed that opioid peptides and serotonin are "pain control substances" (13) which act as blockers of pain information in the synapses of afferent pathways of pain, e.g., in the synapses of the nucleus reticularis gigantocellularis (NRGC), periaqueductal gray matter (PAG), thalamus, and the posterior horn of the spinal cord.

This study was undertaken to examine analgesic effects of phenylethylamine analogues, PEA, amphetamine, OHPEA and (3-hydroxyphenylalanine (OHF) (Table 1), and to elucidate the mechanisms of their analgesic action, especially the correlation of the analgesic action to serotonergic neurons and endogenous opioid peptides.

**Materials and Methods**

Male ddY mice, weighing 17 to 20 g, were used. Pain thresholds of mice were measured by using the hot plate method of Woof-MacDonald (14). The hot plate was maintained at a temperature of 55±0.5°C by using a thermistor. In order to determine pain thresholds of mice, the latency, the length of time which mice placed on the hot plate required to initiate any one of the following behaviors, jumping or shaking, licking, holding or lifting their paws, was measured in a room kept at 24±1°C, kept at 55±5% relative humidity and protected from external noise. Prior to the experiments, mice were tested twice for the latency, and those showing a latency ranging from 3 to 10 sec were used for the experiments.

Amphetamine sulfate (Zedrin, Takeda Chem. Industries), DL-β-hydroxy-phenylethylamine (OHPEA, Sigma), β-phenylethylamine hydrochloride (PEA, Tokyo Kasei) and β-hydroxyphenylalanine monohydrate (OHF, Banyu Pharmaceutical Co., Ltd.) were used as PEA derivatives; and pargyline hydrochloride (Nakarai Chemicals), naloxone hydrochloride (Sankyo Co., Ltd.), DL-p-chlorophenylalanine (PCPA, Nakarai Chemicals), reserpine (Tokyo Kasei) and methysergide hydrogenmaleate (Sandoz) were used as pretreatment drugs. Excepting reserpine and PCPA, all drugs were dissolved in 0.9% saline. OHPEA solution was adjusted to approximately pH 7 by adding diluted hydrochloric acid. Pargyline, naloxone and methysergide were injected intraperitoneally 16 hr, 15 min and 1 hr before the administration of PEA analogues, respectively. Reserpine was suspended in peanut oil and injected subcutaneously twice at 2 mg/kg each, 24 and 48 hr prior to the injection of PEA.

**Table 1. Chemical structures and abbreviations of phenylethylamine derivatives**

| Compounds                     | Chemical structure                                    | Abbreviation |
|-------------------------------|-------------------------------------------------------|--------------|
| β-Hydroxyphenylalanine        | ![OHF chemical structure](image)                      | OHF          |
| β-Hydroxyphenylethylamine     | ![OHPEA chemical structure](image)                    | OHPEA        |
| β-Phenylethylamine            | ![PEA chemical structure](image)                      | PEA          |
| Amphetamine                  | ![AM chemical structure](image)                       | AM           |

The raphe magnus (RAM). On the basis of these findings, it is widely believed that opioid peptides and serotonin are "pain control substances" (13) which act as blockers of pain information in the synapses of afferent pathways of pain, e.g., in the synapses of the nucleus reticularis gigantocellularis (NRGC), periaqueductal gray matter (PAG), thalamus, and the posterior horn of the spinal cord.
analogues. PCPA was suspended in 0.9% saline with addition of Tween 40 and injected intraperitoneally twice at 300 mg/kg each, 24 and 48 hr before the PEA-analogue administration. Examples of the time schedule for the pretreatments, PEA-derivative treatments, and the measurement of analgesic activity and the protocol of the experiments are shown in Table 2.

### Table 2. Protocol for the administration of drugs and measurement of analgesic threshold

| Treatments with drugs | Name of groups |
|-----------------------|----------------|
| PCPA or Vehicle       | Control        |
| 0 or Sal              | AM             |
| 15 or Sal             | RP+AM          |
| 30 or 45 or 60 or 90 or 120 (min) | x X x X X X X X X X X |

### Results

**Analgesic activity of PEA derivatives:** All of the doses of amphetamine, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 4 mg/kg and 8 mg/kg, significantly prolonged latency when injected intraperitoneally. The effect of amphetamine developed rapidly after its administration and lasted for 90 min (Fig. 1). Latency reached a
maximum when the dose of amphetamine was 2–4 mg/kg, but diminished at doses over 8 mg/kg.

PEA failed to increase the latency at a dose of 10 mg/kg i.p. dose (Fig. 2b), but significantly increased the latency at a dose of 50 mg/kg 15 min after the injection (Fig. 2a). Intraperitoneal injection of 50 mg/kg of PEA caused an increase of motor activity, exophthalmos and salivation 5 min after the administration. Expression of symptoms reached a maximum 15 min after the injection and lasted for about an additional 15 min. Significant increase of grooming was observed in a period between 20 min and 40 min after the injection. Motor activity was declined in a period later than 40 min after the injection, and the mice were rather sedative during this period.

Intraperitoneal injection of 10 mg/kg of phenylethylamine (PEA) with or without pargyline on latency and effect of naloxone on PEA-induced analgesia. Pargyline (PAR) and naloxone (NX) were pretreated 16 hr and 15 min before PEA injection, respectively. Each point represents the mean value of six mice (a) or eight mice (b). Vertical bars show the S.E. Symbols represent: ○: control; ●: PEA, 10 mg/kg i.p.; ×: PEA+NX; Δ: NX in (a) and ○: control; ●: PAR+PEA, 10 mg/kg; ×: PAR+PEA+NX; Δ: PEA, 10 mg/kg in (b). Significant difference from the control by Student's t-test: **P<0.01, *P<0.05; and significant difference from (a) PEA or (b) combined use of PEA and pargyline: ††P<0.01, †P<0.05.
OHPEA caused a slight increase in the latency 15 min after the injection. However, the increase was not statistically significant. Fifty mg/kg of OHPEA produced a significant increase in the latency 15 to 60 min after the i.p. injection (Fig. 3). OHPEA (50 mg/kg i.p.) induced prolonged exophthalmos in a period between 5 and 45 min after the injection, marked salivation between 5 and 15 min, and sedation between 15 and 45 min. Ten mg/kg of OHPEA also induced salivation.

OHF (250 mg/kg i.p.) had no effect on the latency (Fig. 4a). OHF (250 mg/kg i.p.) induced no significant behavioral change except for slight sedation observed 60 min after the injection.

**Effect of pargyline on analgesia induced by PEA derivatives**: Ten mg/kg of PEA induced no increased latency per se, but produced salient prolongation of the latency between 15 and 30 min after the injection of PEA to mice pretreated with pargyline (100 mg/kg i.p.) (P<0.01) (Fig. 2b). Pargyline diminished the PEA-induced increase of motor activity, but potentiated the PEA-induced salivation. Prolongation of latency by 10 mg/kg of OHPEA was slight, but in mice pretreated with pargyline, it was significant at a period

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**Fig. 3.** Effect of OHPEA with or without pargyline on latency and effect of naloxone on OHPEA-induced analgesia. Pargyline (PAR) and naloxone (NX) were pretreated 16 hr and 15 min before OHPEA injection, respectively. Each point represents the mean value. Vertical bars show the S.E. Symbols represent O: control (8); ●: OHPEA, 50 mg/kg i.p. (7); ×: OHPEA+NX (7) in Fig. 3a and O: control (8); ●: OHPEA, 10 mg/kg+PAR (8); ×: OHPEA+PAR+NX (8); Δ: OHPEA, 10 mg/kg i.p. (9) in Fig. 3b, where figures in parenthesis indicate the number of mice. Significant difference from the control by Student's t-test: **P<0.01; *P<0.05; and significant difference from (a) OHPEA or (b) combined use of OHPEA and pargyline: ↓↓P<0.01. ↓P<0.05.

**Fig. 4.** Effect of combined use of pargyline and OHF on latency (a) and effect of naloxone on analgesia induced by concomitant use of pargyline and OHF (b). Pargyline (PAR) and naloxone (NX) were pretreated 16 hr and 15 min before OHF injection, respectively. Each point represents the mean value. Vertical bars show the S.E. Symbols represent O: control (7); ●: PAR+OHF (8); Δ: OHF, 250 mg/kg (6); Δ: PAR (8) in (a) and O: control (7); ●: PAR+OHF (7); ×: PAR+OHF+NX (7); Δ: NX (7) in (b), where figures in parenthesis indicate the number of mice. Significant difference from the control by Student's t-test: **P<0.01; *P<0.05, and significant difference from combined use of OHF and pargyline: ↓↓P<0.01.
between 15 and 30 min after the OHPEA injection (Fig. 3b). Pargyline potentiated both sedation and salivation induced by OHPEA. OHF (250 mg/kg i.p.) produced no analgesic effect per se, but did following the pretreatment with pargyline (P<0.01). As shown in Fig. 4a, the analgesic effect produced by a combined use of OHF and pargyline was very slow in its onset as it appeared only about 60 min after the injection, lasting for another 30 min. Pargyline potentiated sedation induced by OHF. Pargyline itself had no significant effect on the latency (Fig. 4a).

Effect of naloxone on analgesia induced by PEA derivatives: Pretreatment with 5 mg/kg of naloxone significantly reversed the prolongation of the latency induced by 0.5 to 8 mg/kg of amphetamine. The naloxone-induced reversal of the latency was observed throughout the period in which amphetamine induced analgesia, i.e., the period between 15 and 90 min after the injection of amphetamine (Fig. 1). Naloxone, however, potentiated an increase in motor activity induced by amphetamine.

Pretreatment with naloxone (5 mg/kg i.p.) significantly decreased the prolonged latency induced by 50 mg/kg of PEA (Fig. 2a). Naloxone potentiated PEA-induced increase in motor activity for the initial 30 min after the injection of PEA, but did not affect the change of motor activity induced by PEA at a period later than 30 min. Naloxone failed to counteract PEA-induced salivation.

Naloxone (5 mg/kg i.p.) inhibited prolongation in the latency induced by 50 mg/kg of OHPEA only during a limited period (Fig. 3a), and exerted no effect on the behavioral change induced by OHPEA.

Naloxone (5 mg/kg i.p.) also partly inhibited the prolonged latency induced by a combined use of PEA (10 mg/kg i.p.) or OHPEA (10 mg/kg i.p.) with pargyline (100 mg/kg i.p.) (Figs. 2b and 3b). Naloxone (5 mg/kg i.p.) completely blocked analgesia induced by a combination of OHF (250 mg/kg i.p.) and pargyline (Fig. 4b), but failed to block the behavioral effects.

Naloxone (5 mg/kg i.p.) itself had no hyperalgesic effect (Figs. 1, 2a and 4b). Naloxone increased motor activity and responsiveness to touch at a period between 10 and 60 min after the injection.

Effect of reserpine on analgesia induced by PEA derivatives: Two pretreatments with 2 mg/kg each of reserpine completely reversed the analgesic effect of amphetamine (4 mg/kg i.p.), PEA (50 mg/kg i.p.) or OHPEA (50 mg/kg i.p.) (Fig. 5). Particularly in mice injected with amphetamine or OHPEA, reserpine decreased latency below the normal level, i.e., produced hyperalgesia in a period later than 60 min after the injection.
of PEA derivatives (P<0.01) (Fig. 5a, b). On the other hand, reserpine failed to inhibit the increase in motor activity induced by amphetamine (4 mg/kg i.p.). In reserpinized mice, OHPEA (50 mg/kg i.p.) provoked increased motor activity between 1 and 15 min after the injection. Major behaviors observed on the hot plate were shaking or holding of a paw in non-reserpinized mice, but jumping in reserpinized mice. Reserpine (2 mg/kg s.c. x2) revealed no effect on latency by itself (Fig. 5a, b).

Effect of PCPA on analgesia induced by PEA derivatives: Two i.p. injections of 300 mg/kg each of PCPA almost completely blocked amphetamine (4 mg/kg i.p.)-induced analgesia (Fig. 6a), but did not affect amphetamine-induced increase in motor activity. PCPA partly inhibited prolongation in the latency induced by a combined use of OHF (250 mg/kg i.p.) and pargyline (Fig. 6c). PCPA partly inhibited analgesia induced by a combined use of OHPEA (10 mg/kg i.p.) and pargyline 15 min after the injection of OHPEA, but conversely increased the analgesic effect of OHPEA after 90 min (Fig. 6b). PCPA significantly inhibited the analgesia induced by OHPEA (100 mg/kg i.p.) or PEA (50 mg/kg i.p.) (Fig. 6d, e). PCPA (300 mg/kg i.p. x2) itself revealed no effect on latency (Fig. 6a, d, e).

Effect of methysergide on analgesia induced by PEA derivatives: Pretreatment with 2 mg/kg of methysergide significantly and 48 hr prior to the PEA analogues. Each point represents the mean value. Vertical bars show the S.E. Symbols represent O: control (8), •: AM, 4 mg/kg i.p. (7), x: PCPA+AM (9), △: PCPA (7) in (a); O: control (6), •: OHPEA, 10 mg/kg+i.p. (6), x: OHPEA+PAR (5), △: OHPEA (6) in (b); O: control (7), •: OHF, 250 mg/kg+i.p. (5), x: OHF+PAR (5), △: OHF (6) in (c); O: control (12), •: PEA, 50 mg/kg (11), x: PEA+PCPA (11), △: PEA (12) in (d); and O: control (10), •: OHPEA, 100 mg/kg i.p. (9), x: OHPEA+PCPA (10), △: PCPA (10) in (e), where figures in parenthesis indicate the number of mice. Significant difference from the control by Student's t-test: **P<0.01, *P<0.05; and significant difference from (a) amphetamine (AM), (d) PEA or (e) OHPEA and combined use of PAR and (b) OHPEA or (c) OHF: △P<0.01, ↓P<0.05.

Fig. 6. Effect of PCPA on prolonged latency induced by PEA analogues. PEA-analogue analgesia was revealed by concomitant use of pargyline (PAR) in Fig. 6b and 6c. PAR was pretreated 16 hr before the PEA-analogue injection, and PCPA injected twice 24
inhibited the prolongation in the latency induced by PEA or 50 mg/kg of OHPEA (Fig. 7a, b). Methysergide (2 mg/kg i.p.) revealed no effect on the latency by itself (Fig. 7a, b).

Discussion

Ueshima (14) reported that in hot plate method shaking, holding and lifting of the paw, which are called “primary reactions”, are partly due to the spinal reflex, but licking and jumping, so called “secondary reactions”, are attributed to upper centers located higher than the spinal cord. For that reason, many investigators engage the jumping of mice as the threshold in the hot plate method. If jumping is employed as a single index of threshold, mice must be exposed to a hot plate for a longer time or at a higher temperature than those necessary when “primary responses” are employed as the indices. For example, when the latency was measured by jumping at 60°C, the latency was gradually increased and finally to more than 2 times as long as the initial latency, since a mouse burns its paws (data not shown). When we carried out the hot plate method at 55°C using all indices including jumping, we could obtain reproducible latency during the observation periods.

Results obtained from the present work are summarized in Table 3. Amphetamine, PEA and OHPEA significantly increased the latency of mice in the hot plate method, suggesting that they possess analgesic action. It is well established that learning of animals causes a change in the jumping threshold (15). However, in our experiments, control mice (vehicle-treated group) did not shorten their latency throughout the observation period since we took advantage of every index like licking and others. Therefore, effects of learning on the latency time can be neglected in our present method. PEA derivatives may have genuine analgesic activity since an increased learning leads to a shortening in the latency, resulting in an apparent decrease in analgesia, and at least amphetamine has been claimed to increase learning ability (16).

Creveling et al. (17) demonstrated that PEA was converted to OHPEA by dopamine-β-hydroxylase. Since the substrate specificity of L-aromatic amino acid-decarboxylase is known to be relatively low, OHF may also be converted to OHPEA by the decarboxylase. Neff et al. (18) reported that PEA was subject to deamination by monoamine oxidase (MAO), and Saavedra and Axelrod (19) evidenced that OHPEA was also metabolized by MAO. Since the analgesic action of OHF, OHPEA or PEA was potentiated by a type B MAO inhibitor, pargyline, these compounds or endogenous substances responsible for the analgesia may be rapidly decomposed by type B MAO. As OHF required about an hour before it produced analgesic action, a metabolite of OHF seems
to be responsible for the analgesic effect. Recently, Chuang et al. (20) reported that amphetamine causes a significant increase in brain PEA content which does not come from α-demethylation of amphetamine. Giardina (4) claimed that amphetamine may produce analgesia through PEA and its derivatives, but direct evidence has not been presented.

Summarizing those findings, PEA and OHPEA are considered to produce analgesia by themselves, while OHF seems to be transformed to OHPEA which is responsible for analgesia. Amphetamine may act via PEA and/or OHPEA.

It is well known that anti-histaminics counteract more effectively exogenously administered histamine than endogenous histamine (21). In addition, opioid receptors have multiple subclasses: μ, δ, κ, σ and ε (22). It is indicated that analgesia is revealed through at least the μ and κ receptors (23, 24). Naloxone is a typical μ-antagonist and blocks analgesia more effectively at the μ-receptor site than at the κ-receptor site (23). Taking these into account, we used a relatively high dose of naloxone, 5 mg/kg. This dosage of naloxone inhibited the analgesic action of amphetamine, OHPEA or PEA, and it also blocked analgesia produced by a concomitant administration of pargyline and OHPEA, PEA or OHF (Figs. 1–4, Table 3). These results indicate that the analgesic action of PEA derivatives is mediated through endogenous opioid peptides. In this case, the possibilities involved are two fold. Analgesia can be produced either by release of endogenous opioid peptides or by inhibition of degradation of the peptides, both of which lead to accumulation of the peptides. Preliminary examination on enkephalinase inhibition suggests that the inhibitory activity of these PEA derivatives seems extremely low, if any.

Reserpine, a depletor of serotonin and catecholamines, completely reversed the analgesia induced by amphetamine, OHPEA or PEA (Fig. 5). PCPA inhibits serotonin synthesis and then depletes the serotonin contents in the brain (25). PCPA inhibited the analgesia induced by amphetamine, PEA or OHPEA and by a combined use of pargyline and OHF or OHPEA (Fig. 6). Methysergide (2 mg/kg) inhibited the analgesic activity of PEA and OH PEA (Fig. 7). Giardina (4) reported that reserpine and PCPA decreased the analgesic activity of OHPEA and PEA in mice pretreated with pargyline. These results are strongly suggestive that PEA derivative-induced analgesia is closely associated with serotonergic neurons.

Both amphetamine and PEA increased the motor activity of mice, but in contrast, OHPEA decreased it. Naloxone increased the motor activity and enhanced PEA-induced increase in motor activity, but it little influenced the changes of motor activity induced

### Table 3. Characteristics of analgesia induced by phenylethylamine derivatives

| Dose mg/kg | Alone | Pretreatment with | NX 5mg/kg | PAR 100mg/kg | PAR 100 + NX 5 | PCPA* 300mg/kg | PAR 100 + PCPA* 300 | RP* 2mg/kg | MS 2mg/kg |
|------------|-------|------------------|-----------|--------------|--------------|----------------|---------------------|------------|----------|
| OHF        | 250   | –                | –         | –            | –            | –              | –                   | –          | –        |
| OHPEA      | 50    | +                | –         | –            | –            | –              | –                   | –          | –        |
|            | 10    | ±                | –         | –            | –            | –              | –                   | –          | –        |
| PEA        | 50    | –                | –         | –            | –            | –              | –                   | –          | –        |
|            | 10    | –                | –         | –            | –            | –              | –                   | –          | –        |
| AM         | 4     | +                | –         | –            | –            | –              | –                   | –          | –        |

NX: naloxone, PAR: pargyline, PCPA: p-chlorophenylalanine, RP: reserpine, MS: methysergide, +: analgesia, –: no analgesia, ↓: decrease of analgesia, ↑: increase of analgesia, *: applied twice, **: OHPEA, 100 mg/kg.
by amphetamine or OHPEA. Our behavioral observations revealed that there was no close correlation between the analgesic and behavioral activities of PEA derivatives.

Holtzman (26) reported that an otherwise inactive dose of naloxone significantly reduced the stimulant effects of amphetamine on avoidance responding and locomotor activity in rats. Dettmar et al. (27) reported that naloxone antagonized both amphetamine-induced increase in spontaneous locomotor activity and amphetamine-induced ipsilateral turning in rats lesioned unilaterally with 6-hydroxydopamine. By contrast, Haber et al. (28) reported that naloxone did not alter amphetamine-induced hyperactivity or stereotypy. In fact, we could not get a unidirectional shift in the results of the interaction between PEA derivatives and naloxone. It has generally been accepted that amphetamine- or PEA-induced increase of motor activity is mediated by catecholamines (6, 29). It is also well known fact that reserpine can not reverse amphetamine-induced increase in locomotor activity (30) which is mediated by dopamine. Reserpine reversed analgesia induced by PEA derivatives including amphetamine (Fig. 5). Preliminary experiments revealed that PEA analogue-induced analgesia was potentiated by haloperidol or chlorpromazine and inhibited by apomorphine. It is highly likely that catecholamines, at least dopamine, might be involved in the analgesia induced by PEA derivatives, but its contribution to analgesia will be minor, if any.

Taken collectively, the results from this work are highly suggestive that amphetamine, OHPEA, PEA and OHF possess a similar characteristic in their analgesic action and produce analgesia with intimate involvement of endogenous opioid peptides and serotonergic neurons.

Acknowledgements: We thank Banyu Pharmaceutical Co., Ltd., for the generous offer of β-hydroxyphenylalanine.

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