# Octopamine and Phenylethylamine Inhibit Prolactin Secretion both *In Vivo* and *In Vitro* (43352)

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*Abstract.* **Trace amines are a group of biogenic amines that are present in neural tissue in concentrations ranging from 0.1 to 100 ng/g. In the present work, we examined the action of two trace amines, octopamine and phenylethylamine, which are found in the hypothalamus, on pituitary hormone secretion in different experimental situations *in vivo* and in dispersed anterior pituitary cells. Both octopamine and phenylethylamine decreased high prolactin levels due to swimming or immobilization stress without affecting other adenohypophysial hormones. With regard to the hypoprolactinemic potencies in the immobilization stress model, it was observed that *p*-tyramine, another trace amine, was as potent as octopamine. Phenylethylamine was the least effective. To evaluate the site of action of the effect described, the three trace amines were tested in dispersed anterior pituitary cell cultures *in vitro*. Tyramine and octopamine reduced prolactin secretion in a concentration-dependent manner, at concentrations of $10^{-8}$ to $10^{-5}$ *M*, whereas the hypoprolactinemic effect observed for phenylethylamine was very weak. In pharmacologic experiments, neither octopamine nor phenylethylamine reduced prolactin release when dopaminergic receptors were blocked. This could mean that their hypoprolactinemic action was mediated through the release of dopamine, or it could be a direct action at a dopaminergic receptor. This is the first description of a specific endocrine action both *in vivo* and *in vitro* for octopamine and phenylethylamine. Further studies are needed to ascertain the physiologic or pathologic implication of these findings.** [P.S.E.B.M. 1992, Vol 199]

Trace amines are a group of biogenic amines that are present in neural tissues in concentrations ranging from 0.1 to 100 ng/g, in contrast with classical amines (noradrenaline, dopamine, and serotonin), whose concentrations are in the microgram range (1). A group of almost 20 compounds have been designated as trace amines (e.g., *p*- and *m*-tyramine, *p*- and *m*-octopamine, phenylethylamine, tryptamine, synephrines, etc.). Since trace amines generally possess a high turnover rate, it has been suggested that they are as actively synthesized as classical neurotransmitters, within the mammalian brain (2–4). It has been shown that they have a role in neurotransmission; this may be a regulatory effect on the action of classical transmitters or a direct effect on certain neurones (5–7).

*p*-Octopamine is an amine of mixed action with both direct and indirect effects (8). It is unevenly distributed within the brain, and the highest concentrations are present in the hypothalamus, followed by the midbrain, spinal cord, and pineal gland (9, 10). There is a peak of *p*-octopamine at 15 days of embryonic development in the rat, a time at which noradrenaline is still undetectable. This peak is of hypothalamic origin (11). It is taken up in noradrenergic nerve terminals, accumulated in storage vesicles, and released together with noradrenaline (7). This raised the possibility that it might act as a neuromodulator of noradrenaline action or as a cotransmitter. Data are available to suggest that *p*-octopamine could have a central role distinct from that of a false sympathomimetic transmitter in mammalian noradrenergic cells. It has a potent activity at neurons that are unresponsive or responsive in an opposite fashion to catecholamines, and

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Received May 30, 1991. [P.S.E.B.M. 1992, Vol 199]
Accepted September 23, 1991.

0037-9727/92/1992-0230$3.00/0

it can be found in tissues that are deficient in noradrenaline (6, 7).

Phenylethylamine is present in the brain, with the striatum containing the highest levels, followed by the hypothalamus (12, 13). High affinity binding sites for [$^3$H]phenylethylamine have been found in the brain, with the highest concentrations of binding sites occurring in the hypothalamus and striatum (14, 15). This trace amine is a substrate for type B monoamine oxidases (16) and has a rapid turnover rate (17). It possesses sympathomimetic activity, causing the release of serotonin (18), noradrenaline (19), and dopamine (19–21). It produces stereotyped behavior (22) and a conspicuous hyperactivity syndrome (23), and it possesses anorectic properties (24). These effects are similar to those induced by amphetamines (methyl-$\beta$-phenylethylamine), thus giving rise to the view that phenylethylamine represents an "endogenous amphetamine" (25).

Up to the present, the effects of *p*-octopamine and phenylethylamine on pituitary hormone secretion had not been examined extensively. In a previous study, we demonstrated that *p*-tyramine, another trace amine, could affect adenohypophysial secretion both *in vivo* and *in vitro* (26–28); in a comparative study, we showed that *p*-octopamine was able to decrease high prolactin levels achieved by immobilization stress (26). As stated above, there are several associations with these trace amines and hypothalamic function: the localization of *p*-octopamine as well as its relation to the noradrenergic system, a system involved in neuroendocrine regulation (29); phenylethylamine's distribution within the brain, the presence of phenylethylamine's receptors in the hypothalamus; its circadian rhythm in the extracellular space of the hypothalamus (30); and its influence on other neurotransmitter systems related to hormone regulation. These facts prompted us to examine the action of *p*-octopamine and phenylethylamine on pituitary hormone secretion in different experimental situations *in vivo* and in dispersed anterior pituitary cells. In some cases, the potency of action was compared with that described previously for tyramine (28).

## Materials and Methods

Adult, male Sprague-Dawley rats (150–250 g body wt) from the Instituto de Biología y Medicina Experimental colony were used. They were housed in an air-conditioned room with controlled lighting (lights on from 0700 to 1900 hr) and were given free access to laboratory chow and tap water. Experiments were always performed between 1000 and 1200 hr to prevent variation due to the circadian pattern of prolactin secretion.

**Swimming Stress.** Animals were weighed and injected intraperitoneally with *p*-octopamine·HCl (Sigma Chemical Co., St. Louis, MO) or phenylethylamine·HCl (Sigma) at the stated doses or with an equal volume of saline solution, and 5 min later they were placed in a water bath (one at a time). The water temperature was 22°C; animals were allowed to swim freely for 5 min, and then they were decapitated. A group of rats was injected with saline solution and left undisturbed for 10 min and then decapitated. Blood was collected and the serum separated and frozen for radioimmunoassay determinations.

**Immobilization Stress.** Fifty-day-old animals were weighed and injected intraperitoneally with the specified dose of *p*-tyramine·HCl (Sigma), phenylethylamine·HCl, or *p*-octopamine·HCl, or with saline solution. They were then placed in immobilizing cages, which consisted of 12 × 4-cm plastic cylinders. Ten minutes thereafter, animals were removed from their cages and decapitated, their blood was collected, and the serum was frozen for radioimmunoassay determinations.

**Interaction with Haloperidol.** *p*-Octopamine·HCl, $\beta$-phenylethylamine·HCl, or *p*-tyramine·HCl, at the stated doses, were injected intraperitoneally 10 min before decapitation. Haloperidol (Halopidol; Janssen, Buenos Aires) was injected intraperitoneally at a dose of 0.1 mg/kg body wt 45 min before decapitation. All drugs were dissolved in saline solution.

**Cell Dispersion and Culturing.** The technique employed has been described by Ben-Jonathan *et al.* (31). Briefly, two or three lactating rats were sacrificed by decapitation and the anterior pituitary was rapidly removed and placed in freshly prepared Krebs-Ringer bicarbonate buffer without $Ca^{2+}$ and $Mg^{2+}$. The buffer also contained 14 m*M* glucose, 1% bovine serum albumin, 2% minimal essential medium amino acids (Gibco), and 0.025% phenol red, with the pH adjusted to 7.35–7.4 with 1 *N* NaOH. This and all other media used for culturing were filtered through a 0.22-$\mu$m membrane filter (Nalgene; Nalge Co., Rochester, NY).

Pituitaries were rinsed with the buffer and cut into 1-mm pieces. The fragments were then incubated in buffer containing 0.2% trypsin for 35 min in a metabolic shaker at 37°C under $CO_2$. After the addition of DNase (1 mg/ml; Sigma) for 2 min, the fragments were washed several times with buffer containing 0.2% lima bean trypsin inhibitor. The fragments were then dispersed into individual cells by gentle trituration through a siliconized pasteur pipet. All glassware was siliconized with Surfacil (Pierce Co., Rockford, IL) and steam sterilized. The cell suspension was then filtered through a fine nylon mesh (160 $\mu$m) and harvested by centrifugation at 120*g* for 10 min.

The cell pellet was resuspended in a medium that consisted of Dulbecco's modified Eagle medium, supplemented with 10% horse serum, 2.5% fetal calf serum, 1% minimal essential medium nonessential amino acids, 10,000 units of micostatin, and 10 mg of gentamicin/ml. Cells were counted by means of a he-

macytometer. The yield for one anterior pituitary was approximately $1.5 \times 10^6$ cells and cell viability, as determined by trypan blue exclusion, was greater than 90%.

Cells were plated in 96-well sterile tissue culture clusters (Costar, Cambridge, MA) and incubated with 300 $\mu$l of Dulbecco's medium in a metabolic incubator at 37°C with 5% $CO_2$ and 95% $O_2$. After long-term incubation (96 hr), cells were washed twice with medium 199 (1.25 g of $NaHCO_3$ per liter; Gibco) to remove all traces of serum. Short-term incubation was performed in 300 $\mu$l of medium 199 containing 1% bovine serum albumin, 0.1% ascorbic acid, and 10 $\mu M$ pargyline (controls) or with increasing doses of *p*-octopamine, dopamine, *p*-tyramine, or phenylethylamine ($10^{-8}$ to $10^{-5}$ $M$) in the same solvent. At the end of incubation, the medium was removed and stored at −20°C until analyzed by radioimmunoassay after appropriate dilution with 0.01 $M$ phosphate-buffered saline with 1% egg albumin. Cell cultures were repeated four times, and each time, experimental groups consisted of four or five wells.

**Serum Hormone Determination.** Prolactin, thyrotropin, and follicle-stimulating hormone (FSH) were determined using kits provided by the National Institute of Diabetes, Digestive, and Kidney Diseases. Results were expressed in terms of $RP_3$ rat prolactin standard.

**Statistical Analysis.** Data were analyzed by one-way analysis of variance (to study variation within each group). When $F$ was significant, Scheffé's test was used to compare the means. Results were considered significant when $P < 0.05$. In *in vitro* experiments, results were expressed as the percentage of control values. The median effective dose ($ED_{50}$) and median inhibitor concentration ($IC_{50}$) were calculated using a four-parameter logistic equation with the GraphPAD InPlot program (GraphPAD Software, San Diego, CA).

## Results

**Effects of Octopamine and Phenylethylamine on Hyperprolactinemia Achieved by Swimming Stress.** Swimming stress increased prolactin values, and preinjection of octopamine or phenylethylamine at the dose of 26.7 mg/kg body wt (free base) inhibited stress-induced prolactin release (Fig. 1). Thyrotropin and FSH were not modified by such treatments (data not shown).

**Effects of Octopamine and Phenylethylamine on Hyperprolactinemia Achieved by Immobilization Stress.** When octopamine and phenylethylamine at the dose of 20 mg/kg body wt (free base) were injected intraperitoneally, and rats were stressed by immobilization, both amines decreased high prolactin values significantly (Fig. 2). At lower doses (10 and 5 mg/kg body wt), phenylethylamine was ineffective in altering prolactin titers, whereas octopamine still decreased prolactin in a dose-dependent manner. When the effect of

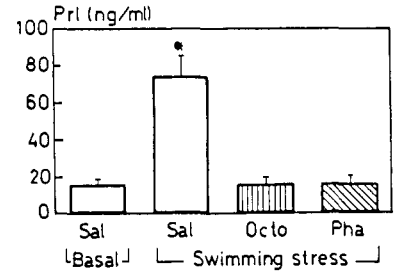


**Figure 1.** Effects of octopamine (Octo) and phenylethylamine (Pha), 26.7 mg/kg body wt (free base), on hyperprolactinemia achieved by swimming stress. Sal, saline-injected controls. For this and the following figures, the height of the bar indicates the mean and the line on top 1 SE. Number of animals per group = 10. * $P < 0.05$ vs Sal Basal.

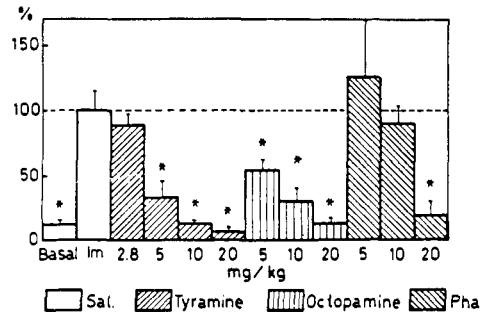


**Figure 2.** Effects of octopamine and phenylethylamine (Pha) on hyperprolactinemia achieved by immobilization stress. The effects of the drugs were compared to the effect of *p*-tyramine. One hundred percent values correspond to immobilized, saline-injected animals (Im). * $P < 0.05$ *vs saline (Sal), immobilized rats.* $n = 10$–$20$ *animals.*

octopamine was compared with that of *p*-tyramine, another brain trace amine, it was found that their effects were not different ($ED_{50}$ 3.82 mg/kg body wt for tyramine and 4.86 mg/kg body wt for octopamine). It is concluded that the relative hypoprolactinemic efficacies *in vivo* are *p*-tyramine = octopamine > phenylethylamine.

Neither phenylethylamine nor octopamine modified luteinizing-hormone or FSH titers (data not shown), though stress by itself lowered FSH values in intact male rates.

**Effects of Octopamine and Phenylethylamine on Haloperidol-Induced Hormone Release.** When rats were injected with haloperidol (0.1 mg/kg body wt), prolactin levels rose significantly (Fig. 3); neither octopamine nor phenylethylamine at a dose of 26.7 mg/kg body wt could counteract haloperidol-induced prolactin release.

**Effects of Octopamine, Phenylethylamine, Tyramine, and Dopamine on Prolactin Release in Adenohypophysial Cells Cultured *In Vitro*.** Trace amines were tested in adenohypophysial cells *in vitro* to evaluate site of action and relative potencies, and to compare with dopamine inhibition of prolactin release.

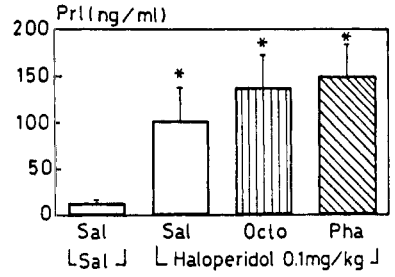


**Figure 3.** Effects of octopamine (Octo) and phenylethylamine (Pha) (26.7 mg/kg body wt) on haloperidol-induced prolactin release. $n$ = 10–12 animals. $^*P < 0.05$ vs saline (Sal)-injected rats.

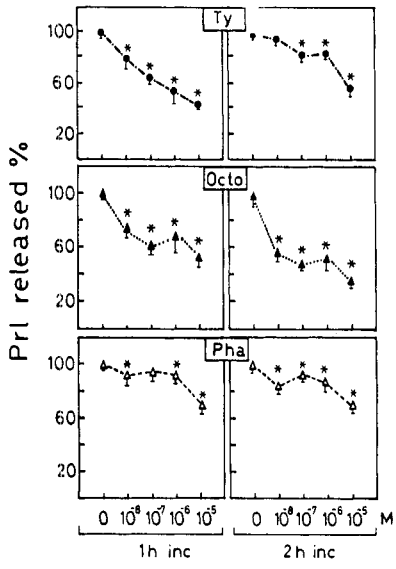


**Figure 4.** Effects of octopamine (Octo), phenylethylamine (Pha), and tyramine (Ty) on prolactin release from adenohypophysial cells cultured *in vitro*, after 1 hr and 2 hr of incubation. $^*P < 0.05$ vs control wells. $n$ = 15–25 animals.

Octopamine effectively inhibited prolactin release by dispersed anterior pituitary cells in a concentration-related manner at the concentrations of $10^{-8}$ to $10^{-5}$ $M$, and at 1 and 2 hr of incubation (Fig. 4).

Phenylethylamine inhibition of prolactin release was less potent than that of octopamine at 1 and 2 hr of incubation.

*p*-Tyramine inhibited prolactin release in a concentration-related way at the concentrations of $10^{-8}$ to $10^{-5}$ $M$ at 1 hr of incubation. At 2 hr of incubation, the concentration of $10^{-8}$ was ineffective.

When the effects of these three trace amines were compared with those of dopamine, it was observed that dopamine was the most effective at 1 hr of incubation ($IC_{50} \pm$ SEM in $M^{-1}$: dopamine, $4.63 \times 10^{-8} \pm 0.16 \times 10^{-8}$; octopamine, $2.08 \times 10^{-6} \pm 0.30 \times 10^{-6}$; tyramine, $9.51 \times 10^{-6} \pm 0.54 \times 10^{-6}$; and phenylethylamine, $>10^{-5}$). At 2 hr of incubation, octopamine and dopamine were the most potent and phenylethylamine had only a weak effect ($IC_{50} \pm$ SEM in $M^{-1}$: dopamine $6.75 \times 10^{-8} \pm 0.12 \times 10^{-8}$; octopamine, $1.73 \times 10^{-8} \pm 0.27 \times 10^{-8}$; tyramine, $2.36 \times 10^{-5} \pm 0.24 \times 10^{-5}$; and phenylethylamine, $>10^{-5}$).

## Discussion

Octopamine and phenylethylamine have been related to neurotransmission as well as to neurovegetative regulation. High levels of *p*-octopamine are associated with genetic hypertension (32), hepatic encephalopathy (33), and Reye's syndrome (34). Also, low levels of this amine have been measured in patients suffering from depression (35); and tricyclic antidepressants, inhibitor monoamine oxidases, and iprindole modify *p*-octopamine turnover in the mouse brain (36), suggesting a role in the etiology of depression. A functional deficiency of phenylethylamine in depressive disorders has also been suggested (37, 38), and it may be excreted in elevated amounts by paranoid schizophrenic patients and by some bipolar-affective patients (37, 39). A number of clinical studies also indicate a possible role of phenylethylamine in extrapyramidal disorders and migraine (40, 41). But up to the present, the participation of phenylethylamine and octopamine in neuroendocrine regulation has not been determined, even though they are present in the hypothalamus and they interact with classical amines involved in hypothalamic hypophysial regulation.

We found that both octopamine and phenylethylamine can decrease high prolactin levels due to swimming or immobilization stress without affecting the release of FSH or thyrotropin. In humans, it has been shown that amphetamine, a metabolite of phenylethylamine, can also decrease prolactin levels as an indirectly acting dopamine agonist (42). With regard to hypoprolactinemic potencies of the trace amines *in vivo*, *p*-tyramine and octopamine are more effective than phenylethylamine. In a previous work (26), we showed that dopamine was more potent than *p*-tyramine in the same experimental model *in vivo*; so it can be assumed that phenylethylamine and octopamine are also less potent than dopamine, a well-established prolactin-inhibiting factor. Nevertheless, the high rate of inactivation of injected trace amines (2–4) must be taken into account when evaluating their hypoprolactinemic action; therefore, though high doses were injected, the effective dose acting at the hypothalamic-pituitary unit is probably lower.

*In vitro*, inactivation of amines was prevented by using pargyline and ascorbic acid in the incubation medium. Both tyramine and octopamine significantly decreased prolactin levels at concentrations ranging from $10^{-5}$ to $10^{-8}$ $M$ at 1 hour of incubation. At 2 hr, octopamine reduced prolactin secretion more effectively than *p*-tyramine. With regard to phenylethylamine, it was clearly shown that its effect was very weak, and, at the concentration of $10^{-5}$, only a reduction of 30% from control values was achieved. This

would indicate that the direct effect of phenylethylamine on lactotropes is minimal, and its inhibitory action on hyperprolactinemia achieved by stress could be indirect, since the drug easily crosses the blood-brain barrier (43).

In pharmacologic experiments, it was found that neither octopamine nor phenylethylamine was active when dopaminergic receptors were blocked. This could mean that their hypoprolactinemic action is indirect and could be mediated through the release of dopamine, which cannot act if receptors are antagonized. On the one hand, this could mean that octopamine and/or phenylethylamine exerts its effects directly on a receptor sensitive to haloperidol. On the other hand, since the mechanism by which immobilization and swimming stress induce prolactin secretion involves the release of a prolactin-releasing factor (44, 45) and not only a disruption of dopaminergic control, the different results described could be suggesting that these amines *in vivo* are interfering with a prolactin-releasing mechanism.

We have described a specific hypoprolactinemic action both *in vivo* and *in vitro* for octopamine and phenylethylamine. Though these are naturally occurring substances within the rodent brain, a physiologic implication in neuroendocrine regulation cannot be ascertained as yet due to their low concentrations. Nevertheless, since these amines vary in a number of pathologic situations (5, 6, 32, 33, 37, 38, 40, 41, 46) as well as in antidepressant treatments (34), neuroendocrine changes occurring in these circumstances could be related to such variations. Also, the novel effect for these amines adds to the growing knowledge of their pharmacologic properties.

This study was supported by Consejo Nacional de Investigaciones Cientificas y Tecnicas (CONICET), Fundación Roemmers, Universidad de Buenos Aires, and John Simon Guggenheim Memorial Foundation.

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