An Orally Active Selenium-Based Antihypertensive Agent with Restricted CNS Permeability

SHELDON W. MAY, LANQING WANG, MICHELLE M. GILL-WOZNICHAK, RICHARD F. BROWNER, ALISON A. OGNOWSKI, JAMES B. SMITH and STANLEY H. POLLOCK

School of Chemistry and Biochemistry, Georgia Institute of Technology and School of Pharmacy, Mercer University, Atlanta, Georgia

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ABSTRACT

We report here the first orally active, selenium-based antihypertensive agent, and we demonstrate its restricted CNS permeability using inductively coupled plasma/mass spectroscopy (ICP/MS) and operant behavioral analysis. The biochemistry and pharmacology of selenium are subjects of intense current interest. As a consequence of the redox chemistry of the selenium moiety, phenylaminalkyl selenides possess the remarkable characteristic of propagating a cycle of turnover-dependent local depletion of reduced ascorbate when processed by the key enzyme of catecholamine metabolism, dopamine-ß-monooxygenase. ICP/MS analysis was used to determine the pharmacokinetic parameters for selenide compounds after i.v. administration to anesthetized rats. Analysis of the data using a two-compartment pharmacokinetic model established very rapid initial clearance and a short beta-elimination half-life from blood. We developed an oxidative procedure for digestion and processing of tissue samples in order to obtain ICP/MS data on the tissue distributions of Se-containing metabolites after the administration of selenide compounds. The results establish that aromatic ring hydroxylation of the selenides results in a marked reduction in brain levels of Se-containing metabolites. The comparative effects of selenide compounds on locomotor activity and operant behavior were then investigated, and the results fully corroborate the ICP/MS analytical results. The novel compound, 4-hydroxy-α-methyl-phenyl-2-aminoethyl selenide, exhibits both restricted CNS permeability and oral antihypertensive activity in spontaneously hypertensive rats. This compound is the first orally active selenium-based antihypertensive agent ever reported, and it possesses properties that are highly desirable in pharmacological agents being developed for treatment of chronic diseases such as hypertension.

The biochemistry and pharmacology of selenium are subjects of intense current interest (Fox, 1992; Parnham and Graf, 1987; Spallholz, 1994; Behne et al., 1995; Beck et al., 1995). Selenium, long known to be an important dietary "antioxidant," is now recognized as an essential component of the active sites of a number of enzymes, and several additional mammalian selenoproteins have recently been identified (Stadtman, 1996; Spallholz, 1994; Behne et al., 1995). Moreover, dietary selenium deficiency has been linked to diseases as diverse as cancer, heart disease, arthritis and AIDS (Clark et al., 1996; Fox, 1992; Parnham and Graf, 1987; Beck et al., 1995).

PAESe was developed in our laboratory as a novel substrate analog for the key enzyme of catecholamine metabolism, DBM (E.C. 1.14.17.1). We have demonstrated that PAESe possesses the remarkable property of initiating and propagating a cycle of turnover-dependent, local depletion of reduced ascorbate, the reductant essential for catalytic turnover of DBM. Experiments both in vitro and in chromaffin granule ghosts have established that DBM-catalyzed selenoxide, followed by nonenzymatic recycling of the selenoxide product, results in local depletion of reduced ascorbate (fig. 1), even in the presence of the b561-dependent ascorbate recycling system of chromaffin granules (May et al., 1987; May et al., 1988; Wimalasena et al., 1989; Herman et al., 1988a). Thus, this unique ability of PAESe to effect DBM-dependent ascorbate depletion is a direct consequence of the redox chemistry of the selenium moiety present in this compound.

DBM is an attractive target point for modulation of peripheral adrenergic activity, and a number of DBM-directed inhibitors and pseudosubstrates have been shown to exhibit antihypertensive activity (Herman et al., 1991; Pollock et al., 1993; Kruse et al., 1986; Herman et al., 1988b). Indeed, we have reported that PAESe exhibits antihypertensive activity when administered i.p. to SHR (May et al., 1988; Pollock et al., 1988). However, as is true for other peripherally acting

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pharmacological agents (Rimmer and Church, 1990; Gilman et al., 1990; Nadellman and Frishman, 1990), the CNS permeability of PAESe is a significant concern because undesirable side effects can often result from CNS penetration.

In this report we demonstrate that HOMePAESe is a selenium-based antihypertensive agent that exhibits both restricted CNS permeability and oral activity. As far as we know, this compound is the first orally active selenium-based antihypertensive agent ever reported. In order to determine the tissue distribution of selenium-containing metabolites—and thus demonstrate the restricted CNS permeability—of HOMePAESe, we developed the methodology introduced herein for reliable, quantitative determinations of selenium in tissue samples using the technique of ICP/MS. In addition, we demonstrate that the analytical ICP/MS data are corroborated by corresponding results from experiments on locomotor activity and operant behavior. Taken together, these results establish that this novel selenium-based antihypertensive compound possesses characteristics that are highly desirable in pharmacological agents being developed for treatment of chronic diseases such as hypertension.

Materials and Methods

Synthesis

HOMePAESe was prepared via a four-step synthesis procedure as follows:

**P-Methoxyphenyl selenol.** Following the general procedure described by Foster and Brown (1928), we added 4-bromoanisole (50 g, 0.27 mol) dropwise to 250 ml of dry ether and 8 g of Mg turnings. The reaction was refluxed for 4 hr under Ar, and then the flask was purged with H2 gas and covered with Al foil. Selenium powder (20.4 g, 0.26 mol) was added slowly, and the reaction was refluxed an additional hour under H2. The reaction mixture was then acidified, and the product (approximately 40% yield) was extracted with ether (200 ml). The ether extract was dried over anhydrous Na2SO4 and evaporated on a steam bath under Ar.

(S)-4-methoxy-a-methyl-phenyl-2-acetamidoethyl selenide. p-Methoxyphenyl selenol was reacted with (S)-2,4-dimethyloxazoline (20 g, 0.20 mol) in benzene by the method of Wehrmeister (1963). (S)-2,4-dimethyloxazoline was prepared using the procedure we have previously described (Padgett et al., 1984). The reaction was refluxed for 12 hr under Ar, and then the crude product (100% yield) was concentrated to dryness: 1H NMR (CDCl3) δ 7.50 (d, 2H), 6.83 (d, 2H), 4.20 (m, 1H), 3.01 (m, 2H), 1.88 (s, 3H), 1.21 (d, 3H).

(S)-4-hydroxy-a-methyl-phenyl-2-aminoethoxyselenide. (S)-4-hydroxy-a-methyl-phenyl-2-acetamidoethyl selenide was demethylated by the procedure of Grieco et al. (1977). Boron tribromide (100 ml of 1 M in CH2Cl2, 0.10 mol) was added dropwise to a stirring solution (10 g, 0.035 mol) in 100 ml of dry CH2Cl2 cooled to ~78°C. The reaction was allowed to warm to room temperature overnight. The product was isolated by pouring the reaction mixture into 100 ml of degassed 4 N NaOH. The aqueous phase was washed with CH2Cl2 and acidified with concentrated HCl. The product (approximately 40% yield) was then extracted with CH2Cl2, dried over anhydrous Na2SO4 and concentrated to dryness: 1H NMR (CDCl3) δ 7.45 (d, 2H), 6.75 (d, 2H), 4.22 (m, 1H), 2.97 (m, 2H), 1.84 (s, 3H), 1.24 (d, 3H).

MePAESe was prepared starting from benzene selenol as described above for HOMePAESe, except that demethylation of the methoxy moiety was obviously not needed. The final product was recrystallized (ethanol/ether) and characterized: decomposition point 180°C; 1H NMR (D2O) δ 7.45 (d, 2H), 7.2 (m, 2H), 3.25 (m, 2H), 2.9–3.1 (m, 1H), 1.24 (d, 3H).

PAESe was prepared as described previously by May et al. (1987).

Selenide Dosing, Sample Preparation and ICP/MS Analyses

Adult male Sprague-Dawley rats were anesthetized with sodium pentobarbital (35 mg/kg i.p.). The left carotid artery and jugular vein were cannulated with heparinized polyethylene tubing, and 7.5 mg/kg selenium was administered into the venous catheter. Blood samples were taken from the carotid artery immediately after drug administration and at various time intervals thereafter using heparinized syringes. Blood was centrifuged at 10,000 rpm for 10 min to remove blood cells, and 0.1-g samples of plasma were used for subsequent analysis. Rats were sacrificed via i.v. pentobarbital overdose, and the brain, lungs, kidney, spleen, heart and liver were...
collected and immediately frozen in dry ice and weighed. Frozen tissues were lyophilized, reweighed and then pulverized to powder with a mortar and pestle.

Tissue samples were prepared for ICP/MS analysis by oxidation using a mixture of concentric nitric acid and 30% hydrogen peroxide in a commercial microwave oven. Replicate 0.05-g lyophilized samples of ground tissue were precisely weighed in capped 60-ml polytetrafluoroethylene vessels, to which 1 ml of trace-metal-grade concentrated nitric acid and 1 ml of 30% hydrogen peroxide were added. One of these vessels was spiked with 50 µl of 10.0 ppm standard selenium in 1% nitric acid solution. Five tightly capped digestion vessels and a bottle filled with 50 ml of water were placed in a microwave pressure cooker. The lidded pressure cooker was put in a commercial microwave oven (Tappan, Model 56-9431-10/04) with a frequency of 2450 MHz, a power output of 800 W and a turntable. The samples were heated using three cycles: 10% power for 8 min, 30% power for 8 min and 60% power for 15 min. The pressure cooker was removed from the microwave oven, cooled and uncovered. After the vessels had cooled to room temperature, the caps were opened to release the produced gas; 10 ml of 4 N HCl was then added, and the vessels were recapped and placed into a 95°C water bath for 20 min. After cooling to room temperature, the digests were quantitatively transferred into 50-ml volumetric flasks and diluted to volume using 4 N HCl. For analysis, each solution was continuously pumped (0.8 ml/min) into a hydride generator, wherein it mixed with a stream of NaBH₄ (1% solution in 0.1 N NaOH pumped at 1.2 ml/min) to form H₂Se, which was swept (using Ar) into a condenser to remove moisture and then into an IC argon plasma coupled to a quadrupole mass spectrometer.

Evaluation of the Effects of Locomotor Activity.

Naive male ND/SW mice were used to evaluate the effects of selenium drugs on locomotor activity. Mice were dosed i.p. (this administration route is widely used in locomotor studies (Prinssen et al., 1996)) with drug or vehicle 30 min before the individual animal was placed in a box (24 cm × 133 cm) that had a grid of lines spaced every 11 cm. The activity of the animals was observed over a 10-min period, during which the number of lines crossed was counted.

Evaluation of Behavioral Effects.

Six experimentally naive male Sprague-Dawley rats were approximately 120 days old at the beginning of the experiment. Water was continuously available in home cages and experimental chambers, and animals were maintained at approximately 300 g b.wt. with a diet of 0.045-g pellets (formula A, P.J. Noyes Co., Lancaster, NH) and Purina Rat Chow.

Experiments were conducted with individual rats placed in a Model C Rat Cage (23 cm long × 20 cm wide × 20 cm high; Gerbrands Corp., Arlington, MA). Each chamber contained a 1-cm-wide translucent disk (G6315, Gerbrands) mounted in the lower right corner of one wall 5 cm above the grid floor, a recessed food cup (F7020, Gerbrands) mounted in the center of the same wall 5 cm above the grid floor and a water bottle and speaker on the opposite wall. The food cup was connected to a solenoid-operated food pellet dispenser (G5100, Gerbrands). The chamber was enclosed in a larger sound-attenuating box, and control and recording of all scheduled events were accomplished with an IBM AT-compatible computer.

The behavior studied was a nose-press of the 1-cm-wide disk, and animals were trained using standard operant conditioning techniques. After initial training with the disk transilluminated by a white light, food pellets were delivered immediately after the first response to occur after 5 min had elapsed in the presence of the white disk (a fixed-interval, or FI, schedule; 5 min). Individual FI segments ended with food pellets or whenever responding failed to occur at the end of a 15-sec grace period after the 5-min period. Individual FI segments alternated with 30-sec periods during which the disk light was turned off and responding did not result in the delivery of food (timeout). Experimental sessions were conducted Monday through Friday, and each session comprised 10 alternating cycles of FI and timeout. Animals responded under the described conditions without receiving any drug until variability of the daily response rates remained within 20% for 2 successive weeks.

MePAESe and HOMePAESe were dissolved in 0.9% sodium chloride and injected i.m. in a volume of 0.25 ml/kg. Sodium chloride vehicle served as the control injection. We find that i.m. is the administration method of choice for behavioral studies; it provides rapid drug uptake from the highly vascularized muscle while avoiding surgical trauma and any associated behavioral complications (Smith, 1991). After initial training and development of stable performance, each animal received at least three injections in mixed order of each of several doses of MePAESe (0.17–10 mg/kg) and HOMePAESe (0.17–30 mg/kg). Drug injections occurred immediately before experimental sessions twice weekly on Tuesdays and Fridays, and vehicle was injected on Thursdays. Each drug has a rapid onset of action when administered i.m., and the immediate preinjection permitted observation of initial behavioral effects. Effects of drugs are shown as an average for each dose in all subjects, and control performance is shown as an average for at least seven vehicle sessions in each subject.

Evaluation of Antihypertensive Activity

Male SHR were purchased from Harlan Sprague-Dawley and fasted overnight. Animals were anesthetized with sodium pentobarbital (35 mg/kg i.p.), and the left carotid artery was exposed, cannulated and exteriorized between the scapulas. Blood pressure was measured directly from the cannula using a P1000B pressure transducer (Narco Biosystems, Dallas, TX). After animals recovered from surgery and a base-line blood pressure was established, they were dosed p.o. with HOMePAESe via a feeding tube. Acute effects were determined by monitoring blood pressure at 15, 30, 60, 120 and 180 min after p.o. dosing. In experiments in which blood pressure was measured for up to 8 to 10 hr, animals were dosed every 2 or 3 hr, and blood pressure was measured every hour.

Statistical Analyses

Data are presented as mean responses ± S.E.M. Two-way analysis of variance for repeated measures was used to test for significance. Comparison of means was performed using the Tukey post-hoc tests. A probability level of P < .05 was considered statistically significant.

Results

Our first objective was to establish that the analytical technique of ICP/MS could be used to determine the pharmacokinetic properties of our selenium compounds. In these experiments, MePAESe, the α-methylated derivative of PAESe (see fig. 2), was administered i.v. to anesthetized rats, and blood was withdrawn from the carotid artery over the next 5 hr. The time course of plasma selenium levels, as monitored by ICP/MS analysis (see “Materials and Methods”), is shown in figure 3. It is noteworthy that using a hydride generator for ICP/MS sample introduction (see “Materials and Methods”) afforded a two orders of magnitude improvement in detection limits as compared with nebulization, as well as superior precision at low selenium levels.

![Chemical structure of PAESe and its derivatives.](image)
(Janghorbani and Ting, 1989). The ICP/MS data in figure 3 were fit to a two-compartment pharmacokinetic model (Gibaldi and Perrier, 1982) and analyzed using PCNONLIN (Statistical Consultants, Lexington, KY). The pharmacokinetic parameters calculated from this analysis indicate a very rapid initial clearance from the blood (alpha-half-life of 20 sec), a short beta-elimination half-life of 63 min and a high apparent volume of distribution (3.6 l/kg). Indeed, as is evident from figure 3, only about 1% of the administered selenium is detectable in plasma at 1 min after drug administration. Thus it is clear that the uptake from blood and the distribution of selenide and its selenium-containing metabolites are accomplished in a highly facile manner.

Although these initial results validate the use of ICP/MS analyses for determination of pharmacokinetic parameters, processing of blood plasma samples as in figure 3 is relatively straightforward. In order to pursue this approach further, it was critical to develop a way to determine reliably the tissue distributions of Se-containing metabolites after i.v. administration of selenium compounds. Accordingly, as detailed in “Materials and Methods,” we developed an oxidative procedure for digestion and processing of tissue samples. Figure 4 shows typical ICP/MS data derived from analysis of tissue samples from normal rats. Figure 4 shows typical ICP/MS data derived from analysis of tissue samples from normal rats. Strong selenium ion beam signals are clearly evident at m/z values corresponding to all four selenium isotopes (as shown in the four panels of fig. 4) after the administration of either HOPASe or MePAESe, brain selenium levels are reduced more than 85% in the case of the ring-hydroxylated derivative, HOPASe. As shown in figure 5, this marked, selective reduction in brain levels of selenium-containing metabolites is apparent for both hydroxylated selenides, HOPASe and HOMePAESe. These results confirm the validity of our design rationale, the assumption that ring hydroxylation in this class of selenides would alter their lipophilicity enough to reduce penetration into the CNS.

These analytical results establish that ring hydroxylation of PAESe derivatives results in a marked reduction in brain levels of Se-containing metabolites, but a compelling basis for drug design can be established only by demonstrating a corresponding reduction in CNS-dependent behavioral side effects. Accordingly, we investigated the effects of PAESe derivatives on locomotor activity and operant behavior.

Figure 6 illustrates the striking difference between the effects of MePAESe and HOMePAESe on locomotor activity in male albino mice. Whereas i.p. injection of MePAESe causes seizures at doses in the 150 mg/kg range, HOMePAESe injection has little or no effect on locomotor activity at all doses examined. The effects of MePAESe and HOMePAESe on operant behavior are illustrated in figure 7. Response rate was decreased almost 70% and animals missed grace-period food deliveries after 1.7 mg/kg MePAESe, and total suppression of response was observed after 10 mg/kg MePAESe (fig. 7, triangles). In contrast, even at the highest dose of HOMePAESe administered (30 mg/kg; fig. 7, circles), response rate was decreased only approximately 40%, and animals contain-
ued to receive all available food pellets. Thus, these behavioral results corroborate the analytical data and confirm the pharmacological relevance of the reduction in brain levels of Se-containing metabolites that we detected using ICP/MS.

We have previously shown that PAESe possesses antihypertensive activity when administered to SHR via i.p. injection (Pollock et al., 1988). The ICP/MS and behavioral results described above clearly suggest that, because of decreased CNS permeability, ring-hydroxylated derivatives of PAESe should be more attractive derivatives than the parent selenide. From a clinical perspective, it is also highly desirable that pharmacological agents used to treat chronic diseases be orally active. We have previously shown that α-methylation of the sulfur analog of PAESe (i.e., PAES) abolishes the activity of the enzyme MAO toward these compounds (Padgette et al., 1984). Because the intestinal mucosa possesses a considerable amount of MAO, resistance to MAO-catalyzed degradation is an essential characteristic for drugs to exhibit good oral bioavailability. Thus the “idealized” selenide, from a pharmacological point of view, would be HOMePAESe. This derivative would be expected to exhibit both oral activity and decreased permeability to the CNS, which would restrict its site of action to the peripheral adrenergic nerve endings.

Figure 8 shows the acute antihypertensive effects of HOMePAESe when given as a single p.o. dose to SHR. This inhibitory effect on blood pressure was dose-related, was observed within the first 30 min of dosing and persisted for 3 hr after drug administration. When the 100 mg/kg p.o. dose of HOMePAESe was administered repeatedly over a period of 8 to 10 hr (fig. 9), the antihypertensive effects were cumulative, resulting in a significant reduction of blood pressure. As expected, there was a greater lowering of blood pressure when HOMePAESe was administered every 2 hr than when...
it was given every 3 hr. Thus the data in these figures confirm that HOMePAESe exhibits marked antihypertensive activity upon p.o. administration in SHR.

**Discussion**

Selenium is now widely recognized as an important “dietary antioxidant” (Walter et al., 1972; Leibovitz et al., 1990; Caldwell and Tappel, 1964) and as an essential element in biological systems. The best-characterized antioxidant role of selenium arises from its presence in the selenocysteine residue of the glutathione peroxidase selenoenzyme family (Stadtman, 1996; Ursini and Bindoli, 1987). In the presence of glutathione, these enzymes scavenge hydroperoxides to prevent cellular damage. Maintenance of the narrow range of selenium intake required to keep an individual healthy is not always possible, and selenium intakes falling outside this range often result in deficiency disease and toxicity (Fox, 1992; Spallholz, 1994). Deficiency of dietary selenium has been linked to a host of diseases, such as heart disease, cancer, diseases of the liver and pancreas, osteoarthritis and, recently, AIDS (Fox, 1992; Parnham and Graf, 1987; Beck et al., 1995). Moreover, Beck et al. (1995) have recently reported the first direct evidence that a virus can mutate and become deadly as a result of selenium deficiency. Thus the pharmacology and biochemistry of selenium are subjects of intense current interest.

The unique ability of the phenylaminoalkyl selenides de-
developed in our laboratory to initiate and sustain a cycle of local ascorbate depletion within adrenergic vesicles is a direct consequence of the redox chemistry of the selenium moiety (May et al., 1987; May et al., 1988; Wimalasena et al., 1989). Initially, DBM present within the vesicle converts these compounds to the corresponding selenoxides in a facile process that proceeds via the normal, ascorbate-dependent oxygenation pathway of DBM catalysis. The product selenoxide is then nonenzymatically reduced back to selenide, with the concomitant and stoichiometric oxidation of reduced ascorbate present in the vesicle to fully oxidized ascorbate. This selenide/ascorbate cycle is a localized process because DBM is present only in these vesicles and because reduced ascorbate does not cross the vesicle membrane. Although adrenergic vesicles possess a cytochrome b_556-dependent ascorbate recycling system, this system can recycle only semidehydroascorbate, which is generated during DBM turnover, and cannot recycle the fully oxidized ascorbate produced by the nonenzymatic selenoxide/ascorbate reaction. Thus the net result of selenide processing in the vesicle is the effective local depletion of reduced ascorbate—an essential cofactor for DBM—and the inhibition of NE production. We have demonstrated this turnover-dependent ascorbate depletion process both in vitro and in chromaffin granule ghosts (May et al., 1988; Wimalasena et al., 1989), we have established cellular and vesicular uptake of the selenides (May et al., 1996), and we have provided evidence that the adrenergic nerve terminal is indeed the pharmacological site of action of PAESe in vivo (Pollock et al., 1988). Moreover, as predicted on the basis of the redox potentials of selenoxides vs. sulfoxides, we have demonstrated (May et al., 1988) that although sulfur-containing analogs undergo DBM-catalyzed oxygenation, they are not capable of propagating such a cycle of ascorbate depletion.

In a previous report, we demonstrated the ability of PAESe to lower systemic blood pressure in SHR after parenteral administration (Pollock et al., 1993). In the work reported herein, we demonstrate for the first time the antihypertensive activity of the hydroxymethylated derivative of PAESe after p.o. administration to conscious SHR (figs. 8 and 9). Hydroxylation limits the accessibility of HOMePAESe to the CNS, whereas methylation on the α-carbon prevents MAO-catalyzed oxidation (Padgette et al., 1984). Because the intestinal mucosa possesses MAO, the major enzyme involved in metabolism of phenylalkylamines, resistance to degradation by this enzyme would certainly be expected to facilitate achieving adequate blood levels of HOMePAESe so as to produce an antihypertensive effect after p.o. administration.

It is well known that the sympathetic nervous system plays an important role in the development of hypertension in SHR (Judy et al., 1976). Therefore, reduced synthesis of the neurotransmitter norepinephrine could explain the antihypertensive effects observed with HOMePAESe. The peripheral adrenergic nerve ending appears to be the site of action for this effect, because HOMePAESe has limited access to the CNS (figs. 5, 6 and 7). Indeed, we have established that the parent compound of HOMePAESe, PAESe, is capable of entering chromaffin granule ghosts and inhibiting formation of norepinephrine via the process illustrated in figure 1 (Wimalasena et al., 1989) and that it also markedly decreases norepinephrine levels in SHR (Pollock et al., 1988).

The duration of the antihypertensive activity of HOMePAESe is short, lasting only 3 to 4 hr (figs. 8 and 9). As expected, shortening the interval of dosing resulted in an increase in hypotensive activity (fig. 9). This may be explained, in part, by the substitution on the aromatic ring. Ring-hydroxylation increases polarity, resulting in compounds that are more readily excreted from the body (Hoffman and Lefkowitz, 1990). In addition, the presence of the hydroxyl group on the ring enhances glucuronide or sulfate conjugation, resulting in the formation of an inactive compound that is readily excreted (Kruse et al., 1987). In a similar study, the duration of the antihypertensive activity of HOMePAESe was found to be short compared with the activity of its methylated derivative (Pollock et al., 1993).

The methodology developed in this work enabled us to utilize ICP/MS analyses to determine both pharmacokinetic parameters and the tissue distributions of selenium-containing metabolites after drug administration. The latter is a much more difficult issue, and the oxidative procedure for digestion and processing of tissue samples reported here followed by sample introduction via a hydride generator provides excellent precision and sensitivity. The results of these determinations offer clear chemical evidence for the restricted CNS permeability of HOMePAESe. This conclusion is fully corroborated by our experiments on locomotor activity (fig. 6) and operant behavior (fig. 7), a result that confirms the pharmacological relevance of the ICP/MS analytical data. Clearly, the issue of CNS permeability is a critical consideration in the evaluation of peripherally acting pharmacological agents, because undesirable side effects resulting from CNS penetration can obviously place severe limits on the clinical potential of such compounds. A familiar example is provided by the H_1-antagonists, where the sedation caused by many early compounds has been greatly mitigated by development of new antihistamines with much lower CNS permeability (Rimmer and Church, 1990). Other examples include the introduction of ipratropium as an atropine replacement that lacks appreciable CNS effects (Gilman et al., 1990) and the development of beta-adrenergic blocking.
agents with reduced lipid solubility (Nadelman and Frishman, 1990).

A few other synthetic selenium-containing compounds have been reported to be undergoing evaluation as potential pharmacological agents. Ebseilen (2-phenyl-1,2-benzoisothiazol-3(2H)-one), which was designed to mimic the enzymatic activity of glutathione peroxidase, is an orally active anti-arrhythmic agent that is currently undergoing clinical testing for the inhibition of stroke (Parnam and Graf, 1991). Both selenazofurin, as an antineoplastic and antiviral agent, and selenotifen, as an anti-allergic agent, are examples of pharmacologically active organoselenium compounds that offer significant advantages over their corresponding sulfur analogs (Parnam and Graf, 1991). In the cardiovascular area, aside from our work with phenylaminoalkyl selenides, the only report is a brief description by researchers in Moscow (Rejholec, 1985) regarding the compound selenolactam, which claims anti-arrhythmic activity in mice with potency superior to that of the calcium antagonist verapamil. However, this initial report has never been substantiated with experimental data. Thus, as far as we know, 4-hydroxy-alpha-methyl-phenyl-2-aminoethyl selenide is not only the first orally active selenium-based antihypertensive compound to be described but also the first documented orally active selenium-based cardiovascular agent of any kind.

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