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Matching to Sample, Blood Pressure and Hormonal Effects of Chronic Enalapril in Baboons

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TURKKAN, J. S. AND R. D. HIENZ. *Matching to sample, blood pressure and hormonal effects of chronic enalapril in baboons.* PHARMACOL BIOCHEM BEHAV **34**(4) 685–690, 1989.—Sensory and behavioral performance of three normotensive and one renovascular hypertensive baboon was tested before, during and following chronic oral dosing with the angiotensin converting enzyme (ACE) inhibitor enalapril. Performance measurements during a five-color simultaneous matching to sample task were obtained during enalapril dosing of 0.18 and 0.61 mg/kg/day, and vehicle. Each dose was administered for 21 consecutive days preceded and followed by 14 baseline and recovery periods, respectively. BP from awake animals as well as serum ACE activity were measured. Systolic BPs decreased by a maximum of 6–8% (8 mmHg). ACE activity was decreased in a dose-dependent fashion by 54.01% and 81.63% for 0.18 mg/kg and 0.61 mg/kg doses, respectively. At 0.61 mg/kg, the duration of simple key-press motor behavior increased by 15% in the first week and then progressively returned to baseline levels. Systematic changes in choice reaction times or color discrimination accuracy were not observed. Although the renovascular hypertensive baboon displayed greater hypotension and ACE inhibition, behavioral effects were not significantly different from normotensive baboons. The present study extends to sensory functions the lack of adverse behavioral side-effects of enalapril.

Enalapril maleate Angiotensin converting enzyme inhibitor Color discrimination Motor behavior Renovascular hypertension Blood pressure Antihypertensive agents Adverse side-effects Nonhuman primates Baboons

ENALAPRIL maleate is one of a popular class of antihypertensive agents that lowers blood pressure (BP) by inhibiting the conversion of the hormone angiotensin I to the potent pressor hormone angiotensin II, thereby preventing the peripheral vasoconstriction and antinatriuretic effects of angiotensin II. Angiotensin converting enzyme (ACE) inhibitors have been used increasingly in the last decade since the ACEs were found to have utility as antihypertensive agents (3). Enalapril has been found to be a longer acting, more potent orally active ACE inhibitor than the more typically prescribed agent, captopril (1).

No clear evidence exists as to the action of peripherally administered ACEs at central nervous system sites (21), and few laboratory studies have assessed the behavioral effects of ACEs (25). One study with normotensive humans found no impairments on a variety of psychomotor and other behavioral tasks or on physiological measures of EEG and skin conductance levels during a 2-week dosing period (18), although some indications of increased arousal were obtained, as indexed by augmented auditory evoked responses and increased tapping rates. A study of recall memory of moderate–severe hypertensive patients found that although 20 mg/day of enalapril significantly lowered systolic and diastolic blood pressures (SBP and DBP) by 47 and 27 mmHg after a 16-week dosing period, memory function was not impaired (13).

The potential sensory effects of enalapril have not been previously studied in the laboratory. The present study was undertaken to examine sensory and motor changes as well as blood pressure and ACE inhibition during chronic oral dosing with enalapril in baboons. Both color discrimination accuracy and motor response times were examined during performance of a simultaneous matching to sample task which has revealed impairments during chronic dosing with the calcium channel blocking agent nifedipine (28).

METHOD

Three adult male baboons (*Papio cynocephalus, hamadryas,* and *anubis*) served as subjects because of: 1) their adaptability to long-term experimental conditions; 2) their similarity to man in terms of circulatory parameters such as blood pressure (BP), heart rate, clinical biochemistry, autoregulation of peripheral vascula-

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ture, and response to vasoactive pharmacological compounds (6, 15, 26, 29); and 3) their similarity to man in terms of their sensory acuity (8). Animals ranged in weight between 26–29 kg, and were housed in individual living cages. Water was continuously available excepting during daily 90-min experimental sessions; 23-hour water intake was measured daily at 9 a.m. After arrival in the laboratory, baboons were trained to present their arm for auscultatory systolic and diastolic blood pressure (SBP and DBP) measurement (27).

Experimental sessions were conducted in a double-walled acoustically attenuating chamber with inner dimensions of $1.07 \times 1.37 \times 1.68$ m. Two flourescent tubes covered with a translucent panel provided diffuse lighting on the ceiling of the chamber. The chamber contained a small cage fitted with a seating bench, and an aluminum intelligence panel fitted at one end (46.7×48.3 cm). Six press-plate manipulanda (BRS) were inserted into circular openings in the intelligence panel and served as both stimulus panels and response keys. The keys were configured such that one key (the sample) was centered above, and five choice keys were placed in a row 14 cm below the sample key and spaced equidistantly (7.6 cm center to center). With the animal seated on the bench, the choice keys were at eye level. All keys could be easily reached from the seating bench. Each key (diameter = 4.4 cm) was transilluminated with an IEEE stimulus projector, and could display either blue, white, green, red, or yellow colors. A computer-controlled food pellet dispenser (BRS) automatically delivered pellets into a food well centered below the row of five stimulus keys. Experimental sessions were automatically controlled and data collected with an Apple IIe computer.

Blood Pressure Measurement

BPs were measured by a technician trained and certified in auscultatory BP measurement with the standard American Heart Association procedure. A small adult BP cuff (bladder dimensions 9.53×17.78 cm) was used for inflation with a mercury manometer. In order to obtain daily blood pressure measurements, baboons were first trained to extend their left arm through an opening in their home cage onto a flat shelf at heart level, and then to sit quietly during auscultatory SBP and DBP (Phase IV) measurement. Small food pellets were used as reinforcers for arm extension, and small chunks of fruit were administered after cuff inflation and deflation was completed. After training was complete, from 2–3 BP measurements were taken on each measurement occasion; these values were then averaged [see (27) for a complete description of training, with frequency distributions of blood pressure displayed]. During chronic dosing, blood pressures were measured at 1 and 4 p.m. Monday–Friday. No differences were obtained as a function of times of day, therefore, BP levels at 1 p.m. are reported here.

Pharmacological Procedures

Enalapril was given orally in order to approximate the clinical conditions under which this drug is normally administered. Drug was supplied in powdered form without cost from Merck (MK-421). Powdered drug was weighed and inserted into ⅓ banana as vehicle. At each drug delivery, the technician observed whether complete ingestion occurred. On no occasion was an animal seen to reject the vehicle + drug; ingestion occurred in less than 5 min. Unlike captopril, food does not alter the absorption of enalapril (24).

Because enalapril's hypotensive effects in baboons are unknown, an initial stage of the study measured SBP and DBPs in baboons after single doses. After a predrug baseline BP measurement, enalapril in vehicle (or vehicle alone) was administered. BPs then were measured at 10, 20, 30, 60, 120, 180, 240, and 300 min after ingestion. These single-dose enalapril administrations were separated by a minimum of 72 hours. Doses studied were 0.18 and 0.61 mg/kg, which span the clinical range for hypertensive patients [range between 0.29–0.57 mg/kg/day, assuming 70 kg adults; e.g., (12,23)]. The technician was blind to drug dose during determinations of single dose-effects on blood pressure, but not during behavioral testing. During behavioral testing, all animals were tested with drug doses in the following order: 0.18, 0.61 mg/kg, and vehicle, administered 45 min prior to testing.

Blood Collection Procedures

The correlation between serum ACE activity and serum concentration of enalapril metabolite (enalaprilat) is high (2). Therefore, in order to indirectly monitor the timecourse of enalapril metabolism during chronic administration and to correlate ACE activity with potential behavioral changes, ACE activity was periodically measured in serum of ketamine anesthetized baboons. Venous blood was sampled during the first week of baseline, during days 5 and 19 of the 21-day drug administration period, and on the day following the final postdrug session for all doses including vehicle. ACE activity was analyzed with spectrophotometric methods [(16), also see (19) for ACE levels in the ketamine anesthetized baboon] at Smith-Kline Laboratories. All samples were coded and split. Assay reliability was high: Pearson $r = .97$, $p < 0.01$.

Behavioral Testing

All baboons were trained to perform a 5-choice matching to sample task composed of individual trials during which animals matched a color to a "sample" key by pressing one of five "choice" color keys. Choice keys were illuminated after the sample key was pressed. Trials began by presenting a flashing (1/sec) sample stimulus color on the sample key. A press on the sample key produced a steady sample color along with 5 different choice colors presented on the choice keys simultaneously (blue, white, green, red, and yellow). A press on the choice key that matched the color of the sample key resulted in all key lights being extinguished and two 190-mg food pellets delivered automatically into the food well. If a nonmatching choice key was pressed, all key lights were extinguished and a 15-sec time-out period ensued where no stimuli were presented and no contingencies were in effect. A 2-sec intertrial interval terminated all trials. Trials following incorrect matches repeated the sample color at the same location on successive trials until a correct match was made. Sample colors were presented according to a randomized block design, and locations of colors on the choice keys were completely randomized. On each trial, data were recorded as to whether an animal successfully matched to a sample color among 5 color choices, and the latency and duration of sample and choice responses. Locations of correct and chosen keys were also recorded. Experimental sessions were conducted for either 90 min or 500 trials, whichever occurred first. Animals experienced behavioral testing sessions once a day Monday–Friday. Each animal was tested at the same time of day across all dose conditions.

For each of the three chronically administered doses studied, testing periods consisted of a 14-day baseline (vehicle alone), a 21-day active dosing period (a constant dose of enalapril administered in vehicle), and a 14-day postdrug period (vehicle alone). Across the 35 experimental sessions in each dose condition, drug or vehicle was delivered once daily, 45 min prior to the testing

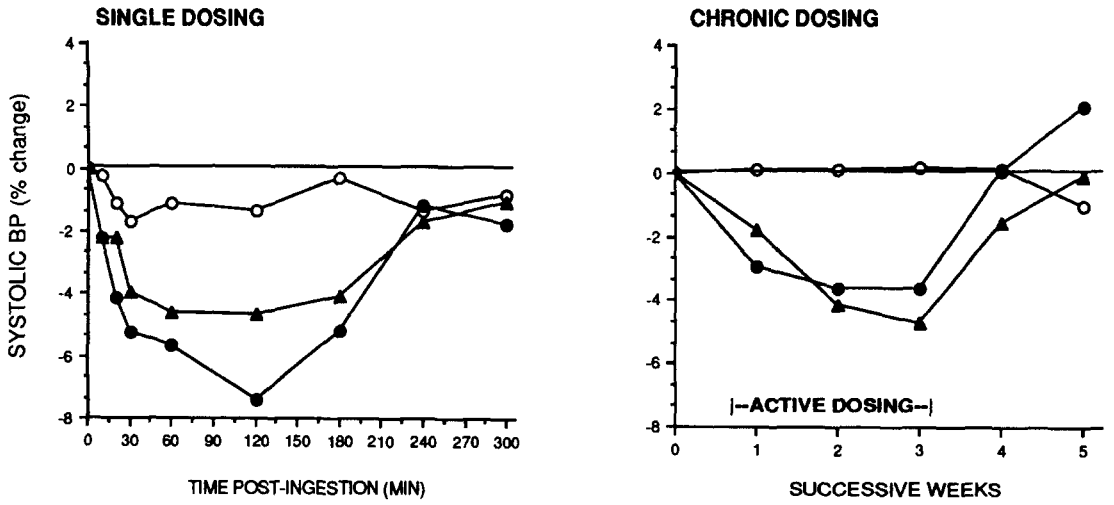

FIG. 1. Systolic blood pressure (mean % change from baseline) as a function of minutes postingestion during single dosing (left panel), and as a function of weeks during and after chronic dosing (right panel). Doses are shown as a parameter. For single dosing, each data point is an individual BP measurement averaged across three normotensive baboons. Percent change is calculated from the systolic blood pressure immediately preceding ingestion. For chronic dosing, each data point is averaged over 5 successive days, over three normotensive animals. Percent change is calculated from the mean of the last 5 days of baseline. ○: Vehicle; ●: 0.18 mg/kg; ▲: 0.61 mg/kg.

session (peak enalapril effects on SBP occurred at 60–120 min during single dosing). On weekends, animals were administered enalapril at 9 a.m.

Data Collection and Analysis

For single-dose BP measurement, systolic and diastolic BPs were calculated as % change from the predrug baseline. Hypothesis testing was carried out with analysis of variance for group, dose, and successive measurements (time-course) factors for both morning and afternoon dosing. For chronic dosing measurements within trials, three dependent variables were measured in hundredths of a sec accuracy during each trial: 1) Press duration on the sample key—the duration that the sample key was depresssed after switch closure; 2) reaction time to select a color match on the choice keys ("choice reaction time"); and 3) the latency to trial initiation ("trial latency") encompassing durations of: time-out when it occurred, intertrial interval, food pellet ingestion, and time to initiate the next trial on the sample key; the latter two durations varied from trial to trial). For these three measures, medians were obtained for consecutive blocks of 50 trials; these were further averaged across blocks 1–3, 4–6, and 7–9. Color matching performance was defined as the number of correct matches divided by the number presented, $\times 100$ ("% correct") for each of five colors in consecutive blocks of 50 trials. Data were excluded from repeated trials after incorrect choices, and from trials or sessions in which there were equipment malfunction.

Data were also averaged across sessions over successive 5-day periods ("weeks"); global hypothesis testing was based on weekly mean percent change from the 2nd baseline week of each dose condition. Analysis of variance was conducted for dose, weeks (3 weeks active dosing followed by 2 postdrug weeks), and within-session timecourse factors. Probability levels less than 0.05 were considered significant. The more conservative Huynh-Feldt probability levels were used to control for violations of sphericity due to repeated measures. Due to the small number of subjects, we also identify "marginally significant" findings which refer to probability levels between 0.055 and 0.10. Planned comparisons were also done of active dosing weeks versus the corresponding week during the vehicle condition.

RESULTS

Baseline Conditions

Baseline average ($\pm$S.D.) SBP/DBP levels of the three normotensive baboons were 116($\pm$11)/60($\pm$3); these levels conform with BP data from femoral arterial catheters in earlier studies [e.g., (26); also see (17) for validation of indirect cuff BP measurement against direct arterial pressures in baboons]. Average ($\pm$S.E.) matching to sample performance over 25 sessions predrug ranged between 95.11($\pm$3.5; yellow)–98.91($\pm$1.0; red) % correct. Baseline average ($\pm$S.E.) press duration, choice reaction time and trial latencies were 53.0($\pm$19.4), 897.8($\pm$61.5), and 837.7($\pm$102.6) msec, respectively.

Drug Effects

Blood pressure.

Single doses. Figure 1 (left panel) illustrates the timecourse of SBP after single doses of enalapril and vehicle. After enalapril ingestion, SBP decreased immediately and reached its lowest level within 60–120 min, followed by recovery to vehicle levels at 240 min after ingestion [timecourse, $F(7,14)=9.25$, $p=0.0002$]. Average decreases at 0.18 mg/kg were (−SBP/−DBP) 6/9, and decreased by 6/7 at 0.61 mg/kg. For SBP only, both doses produced significantly greater BP decreases than vehicle, $F(2,4)=24.38$, $p=0.006$; note the smaller BP decrease after the higher dose, perhaps due to tolerance development after the first, lower, dose was tested. The timecourse of BP decrease and recovery were not different among doses ($p>0.10$) either for SBP or DBP.

Chronic dosing. SBP decreased in the first week of active dosing (Fig. 1, right panel), and reached its lowest level (−6/−3 mmHg) in the third week of dosing [dose $\times$ week, $F(8,16)=16.86$, $p<0.0001$]. SBP change from baseline during vehicle was significantly different from change during active dosing during all active

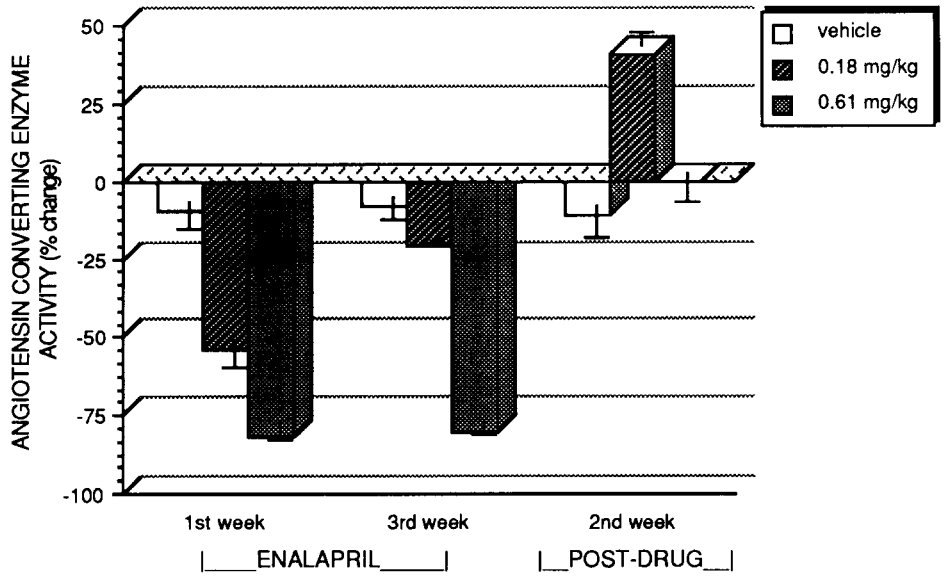

FIG. 2. Serum ACE activity (mean % change from baseline) during the first and third weeks of dosing, and after the final postdosing week. Doses are shown as a parameter. Each column is an average (±S.E.) of two split samples over three normotensive baboons.

dosing weeks (all exact t's $p<0.01$). SBP returned to baseline by the second postdrug week. DBP was not significantly decreased in relation to vehicle.

Angiotensin converting enzyme activity. ACE activity was immediately decreased by enalapril in a dose-dependent fashion, $F(2,4)=13.84$, $p=0.04$. Figure 2 shows the timecourse of change in ACE activity as a function of dose, and illustrates that ACE inhibition was greatest at 0.61 mg/kg [mean maximum % decrease = 81.63%(±3.64)] in comparison to 0.18 mg/kg (54.01% ±8.19) and vehicle (9.37% ±8.6), at both timepoints. ACE activity returned to vehicle levels after active dosing was terminated for two weeks [dose × week, $F(4,8)=31.07$, $p=0.0001$] for both 0.18 and 0.61 mg/kg, although an overshoot occurred in ACE activity above baseline after termination of the lower enalapril dose. Baseline levels of SBP, DBP or ACE activity were not correlated with the subsequent degree of ACE inhibition or levels of ACE activity (all Pearson r's<0.59).

Reaction time. Press duration was significantly lengthened by enalapril in comparison to vehicle (Fig. 3): During vehicle, press duration progressively decreased across study weeks by an average of 20.60(±8.87) msec from the first baseline week to the final week. During active dosing, enalapril increased press durations, although the week of peak effect was dependent on dose [dose × week, $F(8,16)=3.93$, $p=0.01$]. At the lower dose of enalapril, press durations increased in the third dosing week; a further examination revealed that this effect was due to one animal's performance, which did not reverse after enalapril was terminated. At the higher dose, press durations increased by approximately 15% in the first week (exact t difference from vehicle = 12.95, $p<0.05$) and then progressively returned to baseline levels in subsequent weeks (exact t's<0.05).

Mean peak increase in press duration over the first 5 session days was 14.43(±5.45) msec. Press durations of all three animals increased by the third day of dosing; increases for two of the three animals were greater than 15 msec while the third animal showed little change.

Choice reaction times and trial latencies were not significantly affected by enalapril.

Color discrimination. Systematic changes in color discrimination accuracy were not obtained during dosing with enalapril in comparison to vehicle performance. A marginal effect on discrimination of the red stimulus was obtained [dose × week, $F(8,16)=2.62$, $p=<0.08$], such that the greatest improvements in performance across study weeks occurred during vehicle (0.6% change from baseline by the final week) in comparison to 0.2% and 0.1% change during dosing at 0.18 and 0.61 mg/kg, respectively.

Enalapril effects in a renovascular hypertensive baboon. In order to examine whether enalapril's behavioral effects were modulated by a hypertensive condition, one renovascular hypertensive baboon (14,28) was administered enalapril at 0.18 mg/kg during the same time period as the normotensive animals. Baboon DE was shipped to this laboratory approximately 3 months after unilateral left renal artery stenosis (2-kidney, 1-clamp) was performed at the Southwest Foundation for Biomedical Research [San Antonio, TX; see (14) for details of the surgical procedures]. Resting BP level (SBP/DBP) of the renovascular hypertensive animal without ketamine anesthesia was 175/139; blood chemistries revealed no differences from the normotensive animals (28). It was hypothesized that because the starting level of BP was high, enalapril's hypotensive effect might be greater, thereby enhancing the behavioral effects produced. Baboon DE followed the same protocol for single and chronic dosing as the normotensive animals for the vehicle and active dosing conditions.

During both single and chronic dosing at 0.18 mg/kg, Baboon DE displayed a greater hypotensive effect than that of the normotensive animals: BP during single dosing decreased maximally by approximately 20/16 mmHg, while chronic dosing yielded maximum BP decreases (average across 5 days) of approximately 8 mmHg. ACE inhibition was also greater, with 76.9% inhibition in the first week of enalapril, and 67.8% in the third week. Behavioral changes during chronic enalapril administration were not evident either for reaction times, or for color discrimination accuracy.

DISCUSSION

Enalapril significantly decreased blood pressure and angioten-

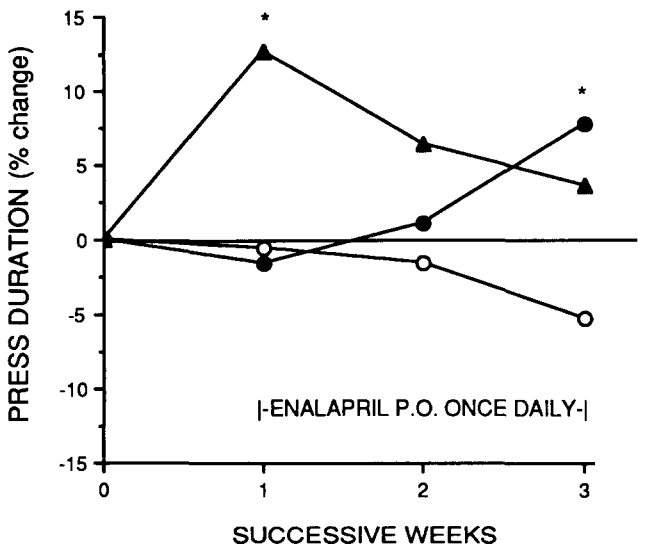

FIG. 3. Press duration (mean % change from baseline) as a function of weeks during and following chronic dosing. Enalapril dose is shown as a parameter. Each data point is based on a median of successive 50-trial blocks, averaged over all blocks, averaged over successive 5-day periods, and averaged over three subjects. Significant differences from vehicle means at the same time point are denoted by * ($p<0.05$). ○: Vehicle; ●: 0.18 mg/kg; ▲: 0.61 mg/kg.

sin converting enzyme activity of normotensive baboons during 21 days of oral dosing in a clinical dose range. Enalapril has been found to be effective in treating hypertensive patients when administered once daily, and BP decreases significantly within 14 days of therapy initiation (7,23). Enalapril also has been effective in lowering BP in renovascular hypertensive animal models (19), as was found for the renovascular hypertensive baboon subject tested here.

ACE activity decreased rapidly in all animals in the first and subsequent weeks of active dosing, verifying that enalapril was effective in blocking formation of angiotensin II (1). At the lower enalapril dose, BP continued to decrease across study weeks, while ACE activity levels reversed toward baseline in the third week and increased above baseline in the post-dosing period. This finding may relate to data from normotensive humans, where repeated exposure to enalapril at 10 mg daily led to a reduction in sensitivity of plasma ACE (11); it has been suggested that prolonged ACE inhibition may induce synthesis of new ACE (11).

Both captopril and enalapril have been widely praised as producing a low side-effect profile in comparison to other antihypertensive agents (12) [see (25) for a review of this literature]. Patients have reported improved quality of life, general wellbeing, and life satisfaction during captopril treatment in comparison to patients who have reported decreased levels when receiving propranolol and alpha-methyldopa (5). Captopril has also been found to have a "mood elevating" effect in depressed normotensive patients (30). Enalapril has been reported to have fewer side-effects than captopril (9). To the extent that mood and quality of life may relate to the ability of patients to function in their daily tasks, the behavioral performance data from the present study confirm that large-scale behavioral performance impairments during enalapril treatment are not evident, at least as assessed within a 21-day dosing period. A study with normotensive human subjects has found increased arousal levels during enalapril, as indexed by faster key-tapping after the first and fourteenth days of dosing, as well as by enhanced auditory evoked response (18). The current study did not obtain improvements in speed of motor responses, and by contrast found increases in (i.e., slower) simple reaction times during the first week of ingestion at the higher dose, which returned to baseline levels by the third week of drug administration. In one of the few animal studies that have examined learned performance after administration of ACE inhibitors, impairments in spatial reversal were found in rats who received an intracerebroventricular injection of captopril, which was suggested to result from disruptions of the putative brain angiotensin system (22).

The sensory effects of the angiotensin converting enzyme inhibitors have not been studied in the laboratory, although self-reports of taste disturbances have been documented for the ACE inhibitor captopril during clinical trials (4), which has not been found during enalapril therapy (12). With regard to visual sensory function, hypertensive patients medicated with captopril have reduced their self-ratings of blurred vision in comparison to methyldopa patients, who increased self-ratings of blurred vision after 24 weeks of therapy (5). A direct assessment of visual function in the current study found that color discrimination accuracy was not impaired during enalapril. During previous testing with the calcium channel blocking agent nifedipine, these baboon subjects showed a 2–4% impairment in color discrimination accuracy in the first week of dosing (28).

The color discrimination and motor side-effects of enalapril appear to be smaller than other antihypertensive agents (25), while the pharmacological effects were significant and marked. Although the time period of drug administration was shorter than is clinically typical, patients often complain of side-effects and drop out of therapy in the first weeks of medication. In conjunction with a low clinical side-effect profile, enalapril deserves further scrutiny as a desirable antihypertensive agent.

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