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Effects of Age on Antidepressant Kinetics and Memory in Fischer 344 Rats[1]

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McMAHON, T. F., M. WEINER, L. LESKO AND T. EMM. *Effects of age on antidepressant kinetics and memory in Fischer 344 rats.* PHARMACOL BIOCHEM BEHAV **26**(2) 313–319, 1987.—Experiments were conducted in young (3–4 months) and old (24–25 months) male Fischer 344 rats to assess the effects of amitriptyline, scopolamine, and zimelidine on short term memory using an eight arm radial maze paradigm. Kinetic analyses employing serial blood sampling were also conducted for amitriptyline and zimelidine in an attempt to determine if age-related deficits in performance could be related to changes in pharmacokinetics. In the maze, acquisition of performance was significantly decreased in old rats compared to young. Amitriptyline (5 mg/kg) produced a significant decrement in maze performance on day four of a five day testing period in both young and old rats, while scopolamine (1 mg/kg) produced an initial decrement on day one, followed by a return towards pre-treatment levels in these two age groups. Zimelidine (5 mg/kg) produced no performance decrement in either young or old rats. Kinetic analyses revealed an increased half-life, slower plasma clearance, and a larger volume of distribution of amitriptyline and zimelidine in old rats. Although the kinetic parameters in aged rats exhibited a change in the direction of a decreased ability to metabolize both drugs, this change was not of sufficient magnitude to produce an additive detrimental effect on maze performance.

Aging Short-term memory 8 Arm radial maze Kinetics Antidepressants

A large body of experimental evidence has accumulated in recent years demonstrating a link between memory impairment and deficits in central cholinergic function in aged humans and animals [27, 28, 35, 40]. Animals that have received anticholinergic drugs [43], cholinergic neurotoxins [42], or surgical lesion of extrinsic hippocampal connections [33] display a marked impairment in behavioral tasks involving short term memory. When the hippocampal neurons of aged rats manifesting behavioral deficits in short term memory are examined electrophysiologically, a significant decrease in firing rate is observed in these neurons compared to young animals [28]. In contrast, when grafts of fetal septal tissue rich in cholinergic neurons are implanted into the hippocampal formation of aged rats with severe impairments in spatial learning abilities, this deficit is partly ameliorated [15].

In humans, disruption of central cholinergic pathways, either by centrally active anticholinergics or as a result of degenerative disease states such as Alzheimer's disease, also results in impairments in memory and cognition [30,31]. For example, in young subjects, low doses of scopolamine cause memory and other cognitive deficits similar to those found naturally in aged subjects tested on the same clinical battery [12]. Diminished cholinergic function in the aged may lead to enhanced central anticholinergic drug effects [4,36]. Thus, the elderly are apt to be more sensitive to centrally active anticholinergics, including those tricyclic antidepressants possessing this property. Indeed, it has been found that antidepressants are among those compounds with central anticholinergic properties which impair memory and cognition in aged humans [9,33]. This point is of therapeutic significance for two reasons. First, the tricyclic antidepressants are among the drugs most commonly used to treat depression in the elderly [22]. While the incidence of depression in the general population is estimated at 10%, it has been reported [3,44] that 20% of elderly people suffer from significant depressive symptoms, while as many as half of all hospitalized elderly patients manifest signs and symptoms of depression. Second, memory loss and/or difficulty with short term memory is a more common clinical feature of depression in the elderly than in young subjects [8,45]. Thus, the use of tricyclic antidepressants in older patients may help relieve depression but at the same time may worsen an already diminished memory capability.

The sensitivity of the elderly to the anticholinergic effects of the tricyclic antidepressants may be compounded by the decreased metabolic capability of the senescent liver [1]. The classic animal studies of Kato [23,24] and more recent investigations in humans [39] have provided evidence that age is an important variable governing the rate of drug biotransformation; further work has demonstrated that the

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changes in metabolism with age are substrate specific [38]. With respect to the tricyclic antidepressants, it has been found that tertiary tricyclics such as imipramine and amitriptyline predominantly undergo N-demethylation to the secondary amines desipramine and nortriptyline, respectively, while secondary amines such as desipramine and nortriptyline are biotransformed mainly by hydroxylation to 2-hydroxydesipramine and 10-hydroxynortriptyline, respectively [1]. Studies of the metabolism of tricyclic antidepressants in elderly humans [1] and rats [10] indicate that demethylation of tertiary tricyclics is more sensitive to the effects of age than hydroxylation of secondary amines, possibly due to age-associated changes in the relative abundance of cytochrome P-450 species [25].

In light of the foregoing information, it was of interest to determine the effects of antidepressant drugs either possessing or lacking significant central anticholinergic properties using an accepted animal model of aging in a behavioral paradigm designed to test short term memory. The present study was designed to assess the effects of amitriptyline (AMI; an antidepressant with significant anticholinergic properties), zimelidine (ZIM; a newer antidepressant lacking such properties) [11], and scopolamine (SCOP; a centrally active antimuscarinic employed as a positive control) in male Fischer 344 rats of various ages on an eight arm radial maze paradigm. A pharmacokinetic profile was also obtained in both age groups through the use of serial blood sampling in an attempt to correlate the effect of drug treatment on maze performance with age-related changes in metabolism of AMI and ZIM.

METHOD

Subjects

Young (3–4 months) and old (24–25 months) male Fischer 344 rats were obtained from colonies maintained by the National Institute of Aging. All rats were given a period of one week to acclimate to their surroundings; during this time, food (Purina Rodent Laboratory Chow 5001) and water were available ad lib. The colony was maintained on a 12 hour (8:30–8:30) light/dark cycle at a temperature of 24±2 degrees C. Rats were first used in a behavioral test of short term memory (eight arm radial maze) and were then employed in a pharmacokinetic experiment involving serial blood sampling after IV administration of the test compounds. All rats were housed upon arrival in stainless steel community cages (51×55×35 cm, Wahmann Mfg. Co., Timonium, MD), 10 rats per cage, on ground corncob bedding (San-I-Cel®, Vivarium Research Inc., White House Station, NJ). Rats were maintained in these cages for the duration of memory testing. Kinetic studies commenced two weeks following the maze experiment, during which time animals were transferred to individual clear plastic cages (47×24×21 cm, without filter tops) with San-I-Cel® bedding and allowed to re-acclimate. Bedding was replaced every other day. During re-acclimation, animals were given free access to food and water, and by the end of this period, body weights had returned to the level of undeprived cohorts. This protocol was employed to obtain the maximum amount of data from each rat and to allow for the determination of correlations between metabolism and behavioral performance.

Behavioral Procedures

An eight arm radial maze was used as one test of short term memory [5,34]. The maze was constructed according to the description given by Watts *et al.* [43]. Training and testing were conducted in a white painted room measuring 4×7 meters which was isolated from environmental noise. The maze was illuminated by a single 75 watt bulb contained within a surgical lighting stand which was positioned over the maze so that the bulb stood approximately 1.5 m over the central platform. All behavioral experiments were conducted between 11:00 a.m. and 5:00 p.m.

For training, rats were put on a restricted food diet until body weight declined to approximately 80% of initial weight in young rats and 75% of initial weight in aged rats. Mean body weight (±SEM) in young rats declined from 197.6±6.1 g to 158.0±4.7 g, while in aged rats mean body weight declined from 407.9±6.2 g to 312.0±6.9 g. This differential level of starvation was employed to produce a more equivalent level of motivation between young and old rats [20]. During this time the rats were introduced to the food (chocolate chips) used as reinforcement in the maze paradigm. Once the rats had been stabilized to 75–80% of original weight and had become accustomed to eating the chocolate chips, daily training sessions (1 session/day) were begun on the maze. Each rat was allowed to explore the maze for 10 min during each training session. Chips were scattered on the maze for the initial sessions, and then placed at increasing distances from the central platform in later sessions when it was apparent that the rats were acquiring the task. Rats were trained on the maze until response level had stabilized for each rat (3 consecutive sessions of 6–8 correct choices) or 15 training sessions were reached. Rats not meeting response criteria by day 15 of training were dropped from the experiment. In this procedure, approximately 75% of young rats acquired the maze task, whereas only 50% of aged rats acquired this task.

Following training, the behavioral effects of AMI, ZIM, and SCOP were assessed in the maze. Saline (SAL) was administered to control animals. Trained rats were randomly assigned to one of the four treatment groups according to a randomization program performed on an Apple IIe computer. On each day of testing, the appropriate compound was administered by IP injection 20 minutes prior to placing the animal on the maze. The number of correct arm entries out of the first eight was recorded for each rat over 5 consecutive days of testing. An arm entry was defined as placement of all four feet into an arm, while an error was defined as re-entry of a previously visited arm or failure to obtain food reinforcement upon entry of a new arm. Doses employed for each compound were as follows: AMI, 5 mg/kg; ZIM, 5 mg/kg; SCOP, 1 mg/kg; SAL, 0.9 mg/kg. The doses of AMI [32], ZIM [21], and SCOP [13] were chosen on the basis of previous reports; in addition, higher doses of SCOP were found to induce fatal tonic-clonic seizures in some of the rats.

Metabolic Determinations

Rats were implanted with indwelling cannulae in the external jugular vein through which the test drugs were given and through which serial blood samples were obtained. Each cannula consisted of a 20 cm length of PE-50 polyethylene tubing joined by heat shrinkable rubber tubing to a variable length of Silastic tubing (0.635 mm i.d., 1.19 mm o.d.; av. length 28 mm). For surgery, each rat was anesthetized with 100 mg/kg ketamine IP, supplemented with inhalations of methoxyflurane when necessary. Following full recovery from surgery, a pre-drug blood sample was obtained from

each rat for use as a blank in analysis. Recovery in young rats was complete by 24 hr; aged rats required 72 hr for complete recovery. Each animal was then given a slow infusion of either AMI or ZIM, 5 mg/kg, through the cannula. Serial determinations were made at 0.5, 1, 2, 4, and 6 hours post-infusion. In some cases a 6 hr sample was obtained by decapitation if the cannula was no longer patent. Blood samples were withdrawn through 23 gauge needles fastened to 1 ml tuberculin syringes. Each sample was approximately 0.3 ml in volume. The samples were placed in 1.5 ml microcentrifuge tubes (VWR Scientific) and plasma was obtained by centrifugation at 8000 rpm for 10 min in a Beckman Microfuge 12.

The mean±SEM plasma AMI and ZIM concentrations for young and old rats were calculated for each sampling point in time except at six hours post-dose for ZIM, where plasma ZIM concentrations were below the level of assay sensitivity in all but one rat. The terminal elimination half-life of AMI and ZIM was calculated by linear regression analysis of the points along the log linear segment of the plasma drug concentration-time curve following intravenous administration. The volume of distribution and plasma clearance were calculated by standard model-independent methods using the area under the plasma drug concentration-time curves [16].

AMI and nortriptyline in plasma were quantitated by enzyme immunoassay (EMIT, Syva Corp.) according to the manufacturer's instructions. Precision of the assay was within 10% for AMI and nortriptyline over the concentration ranges encountered in the study. For analysis of ZIM and norzimelidine, plasma (0.1 ml) and internal standard were alkalinized with 1.5 M NaOH and extracted with an ether-hexane (4:1) mixture. The organic phase was extracted further with a solution of 9 mM dimethyloctylamine in 0.1 M perchloric acid (0.2 ml). Aliquots of this solution were assayed by reversed phase ion-pair HPLC utilizing a 3.9 mm × 15 cm μBondapak C18 column (Waters Associates, Milford, MA). The mobile phase, adjusted to pH 2.6 with 70% perchloric acid, consisted of water:acetonitrile:0.1 M sodium perchlorate (72:20:8) to which dimethyloctylamine (1.9 ml) was added. The mobile phase was pumped at a flow rate of 1 ml/min and detection was monitored at 254 nm. The assay was linear from 53 ng/ml to 3.2 μg/ml, with a sensitivity of 20 ng/ml. The interday and intraday precision was approximately 7% throughout the range of concentrations for both ZIM and norzimelidine.

Chemicals

AMI was obtained as amitriptyline HCl from Sigma Chemical Co., St. Louis, MO. SCOP was obtained as a 0.5 mg/ml solution in the form of scopolamine hydrobromide from Burroughs Wellcome Co., Tuckahoe, NY. ZIM was obtained as zimelidine HCl from Astra Lakemedel Research and Development Laboratories, Sodertalje, Sweden. Ketamine was obtained as ketamine HCl (Ketalar, 50 mg/ml) from Parke-Davis, Morris Plains, NJ. AMI and ZIM were dissolved in 0.9% saline to a concentration of 5 mg/ml and administered in a volume of 1 ml/kg.

RESULTS

Eight Arm Radial Maze

Figure 1 illustrates the acquisition of the maze task by young and old male Fischer 344 rats. In the first five trials, young rats acquired the maze task at a faster rate than aged rats. However, after day 5, the rate of acquisition was similar between the two age groups, although the final level of performance attained by the aged rats was lower than that of the young rats (Fig. 1). Figure 2 shows the performance of the young and old rats on the eight arm radial maze according to the treatment received. Data were analyzed using a two way mixed factorial ANOVA with trials as the repeated measure. As expected, SAL did not produce any performance decrement over the five day testing period in either age group. SCOP, employed as a positive control, produced a reversible decline in performance in both age groups which was significant for young but not old rats. ZIM did not produce a significant decrement in performance over the testing period; however, a slight increase in performance was noted by day five of testing in young rats. A significant difference in over-

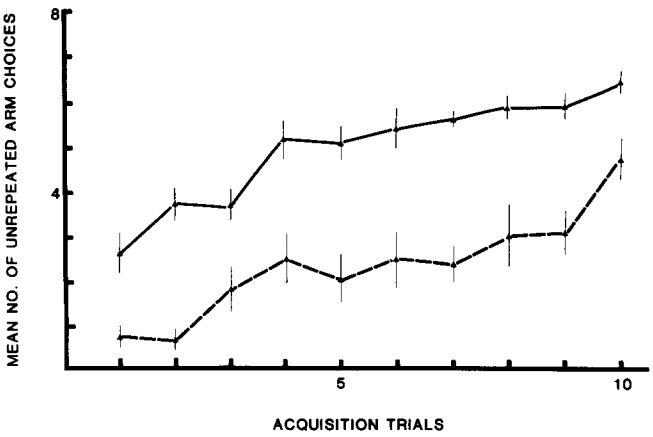

FIG. 1. Acquisition of maze performance in young (—) and old (— — —) F344 rats. Each data point represents the mean SEM for 30 animals in each age group. All values for the old rats are significantly different from young, $F(1,59)=22.92$, $p \leq 0.01$.

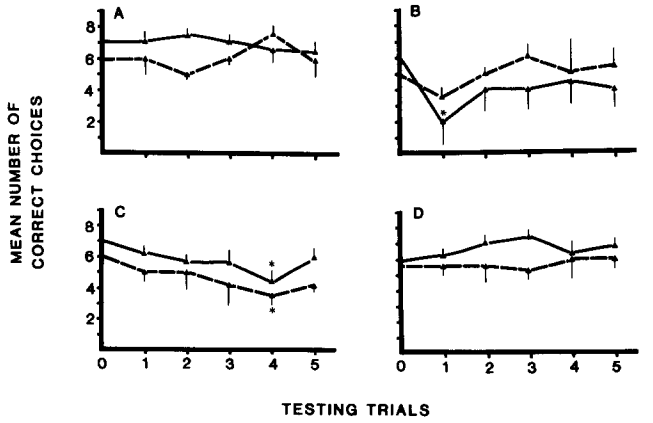

FIG. 2. Maze performance in young (—) and old (— — —) F344 rats treated with SAL (panel A), SCOP (panel B), AMI (panel C), and ZIM (panel D) for five days by daily IP injection. Each point represents the mean SEM for 3–4 rats of the number of correct choices on the indicated test day, according to treatment. Pre-treatment SEM is less than 5% of the mean in young rats and less than 6% of the mean in old rats. *$p<0.05$ vs. day 0 by Dunnett's test; day 0=pre-test level of performance.

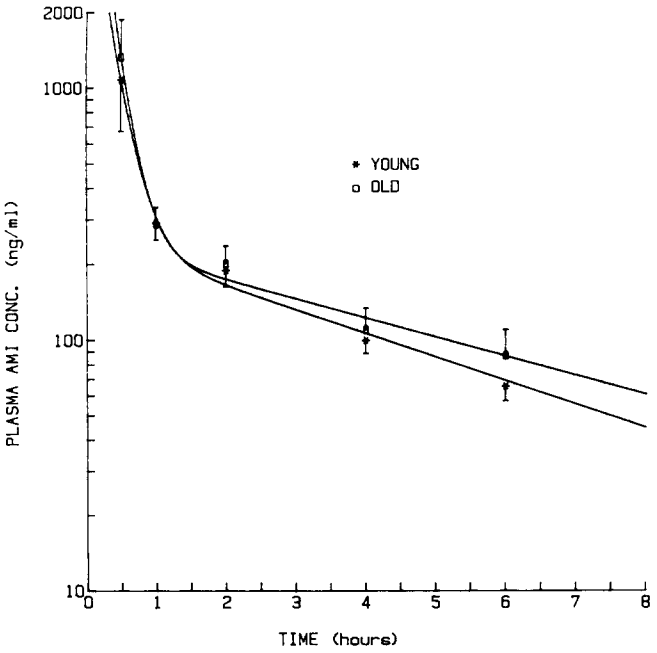

FIG. 3. Plasma AMI concentrations (mean±SEM) in young (N=4) and old (N=3) F344 rats obtained following administration of 5 mg/kg AMI by intravenous infusion into the external jugular vein.

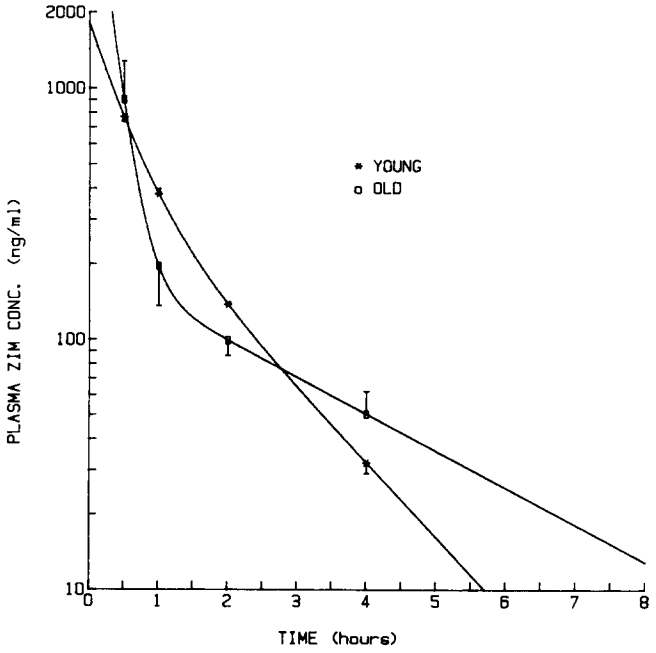

FIG. 4. Plasma ZIM concentrations (mean±SEM) in young (N=4) and old (N=3) F344 rats following administration of 5 mg/kg ZIM by intravenous infusion into the external jugular vein.

TABLE 1

PHARMACOKINETICS OF AMI AND ZIM IN YOUNG AND OLD FISCHER 344 RATS

		Drug	
Variable	Age	AMI	ZIM
Elimination half-life (hr)	Young	3.4 ± 0.4	0.77 ± 0.01
	Old	5.8 ± 1.3	1.7 ± 0.3*
Volume of distribution (l/kg)	Young	10.3 ± 2.3	5.0 ± 0.25
	Old	10.8 ± 1.3	10.4 ± 5.5
Clearance (ml/kg/min)	Young	35.8 ± 7.8	74.0 ± 2.5
	Old	26.4 ± 10.3	61.3 ± 24.9

The effects of age on pharmacokinetic parameters were determined from serum obtained and analyzed as described in the Method section. Values represent the mean ± SEM for four or three rats in the young or aged group, respectively. *$p<0.05$ compared to young rats by Student t-test, two-tailed.

TABLE 2

PHARMACOKINETICS OF NORTRIPTYLINE AND NORZIMELIDINE IN YOUNG AND OLD FISCHER 344 RATS

		Metabolite	
Variable	Age	Nortriptyline	Norzimelidine
Cmax (ng/ml)	Young	45.1 ± 7.45	2557 ± 156
	Old	36.8 ± 1.7	1709 ± 497*
Tmax (hr)	Young	0.50 ± 0.02	1.25 ± 0.25
	Old	0.67 ± 0.15	2.70 ± 0.71*
AUC Ratio (metabolite/parent)	Young	0.04 ± 0.01	7.90 ± 0.35
	Old	0.03 ± 0.02	3.60 ± 0.95*

The effects of age on pharmacokinetic parameters were determined from serum obtained and analyzed as described in the Method section. Values represent the mean ± SEM for four or three rats in the young and old group, respectively. *$p<0.05$ compared to young rats by Student t-test, two-tailed.

all performance due to age was noted in those rats receiving AMI; this difference was significant for the entire testing period. In addition, measurement of performance on day four in both young and old rats and analysis using Dunnett's test showed that AMI produced a significant decline from control (day 0). Mean choice accuracy declined from 6.7 to 4.5 correct choices on day four in young rats, and from 5.7 to 3.5 correct choices in old rats. Trend analysis employing coefficients of orthogonal polynomials showed a significant linear trend of decline across five days for the young rats, $F(3,15)=3.37$, $p<0.05$. Such a trend was not observed in the old rats.

Serial Blood Sampling

Plasma concentration curves for AMI and ZIM in the young and old age groups of rats are shown in Figs. 3 and 4, while the results of kinetic analysis in these same rats are presented in Table 1. Although not significantly different, there was a tendency towards an increased half-life of elimi-

nation, a slower plasma clearance, and an increase in the amount of AMI in the "tissue" compartment in the old animals treated with AMI. These changes were similar for those rats given ZIM. However, in the case of the half-life of elimination for ZIM, this change did reach statistical significance.

Levels of norzimelidine reached peak serum concentrations at 1–2 hours in young rats, and at 3 hours in aged rats; in addition, young rats showed significantly higher levels of norzimelidine in plasma at 1 and 2 hours post-infusion. In contrast to norzimelidine, there were no age-related changes in the rate of formation of nortriptyline, as evidenced by similarities in the Cmax, tmax, and AUC ratio values (Table 2). For every parameter measured, there was a corresponding shift in the old animals in the direction of a decreased metabolic capacity for AMI and ZIM.

DISCUSSION

In this study, the antidepressants AMI and ZIM were investigated for their effects on short term memory using Fischer 344 rats of varying ages in an eight arm radial maze paradigm. A pharmacokinetic profile was also obtained in these animals to determine if age related changes in the kinetics of AMI and ZIM could account for differences in the effect of the drugs on performance on the maze. It was anticipated that the use of compounds with significant central anticholinergic effects would disrupt the memory processes required for normal functioning in the eight arm radial maze paradigm while those compounds lacking such a property would not interfere with performance. The results of the maze experiment demonstrated that those rats receiving AMI did manifest a performance decrement over the testing period while the ZIM treated rats were not adversely affected. Those animals receiving SCOP as a positive control exhibited the most marked impairment in performance on day one of treatment, with a subsequent gradual rise towards pre-treatment levels during days 2–5. Similar results have been obtained by other investigators using SCOP in the eight arm radial maze. Eckerman [13] demonstrated a dose-related decrease in choice accuracy in rats given a single injection of SCOP while Stevens [41] reported a significant decline in mean number of unrepeated arm choices in rats treated with SCOP, 0.3 mg/kg/day, over a 15 day testing period. The results of this latter study are in agreement with the present data, in that the most severe impairment in performance was observed on day one of testing, followed by an increase in the number of correct choices on days 2–5. Furthermore, young rats displayed a pattern of continued decrement over the five day testing period, although in contrast to Stevens, this decrement did not remain significant.

Age itself did not appear to result in dramatic differences in performance as reflected in the lack of significance in performance between age groups in SAL-treated rats. The administration of drugs with centrally active anticholinergic properties, however, clearly had an effect, in that disruption of maze performance occurred in both age groups. Aged rats, however, appeared less sensitive than young rats to memory disruption caused by SCOP or AMI, as reflected in the lack of a significant effect in SCOP-treated aged rats and the lack of a significant trend of decline in performance in AMI-treated aged rats. This data is in agreement with that of Pedigo *et al.* [35], in which aged rats were found to be less sensitive than young rats to the locomotor activating effect of SCOP. Collectively, these findings contrast with the generally observed decline in cholinergic function which is observed with age [4,35], and its association with memory impairment. It is possible that the decreased sensitivity of aged rats to drug treatment is merely a reflection of their inability to achieve the same performance level on the maze as the young rats, in which case anticholinergic drug effects would appear to be less prominent. Thus, although elderly humans may be more susceptible to memory and other cognitive deficits associated with the administration of compounds possessing central anticholinergic properties such as tricyclic antidepressants [19,26], the present results with aged rats using a radial maze paradigm do not lend support to this idea.

Age-related impairment in the performance of aged rats on the eight arm radial maze may not be solely related to cognitive deficits. For instance, differences in motivation may contribute to differences in maze performance between young and old rats. The incorporation of differential food deprivation into the experimental paradigm was intended to minimize the possible contribution of this factor. Previous studies have shown that such a regimen is effective in reducing this difference [20]. The level of general and exploratory activity is also known to be reduced in aged rats [17]. This may account for the initial low rate of responding in the maze task by the aged rats. However, once the task was acquired, response times of the aged rats in this study were equivalent to those of the young rats.

Based upon previous studies which have demonstrated age-related decreases in NADPH-dependent metabolism of various drugs [23,24] and various components of the microsomal monooxygenase system [38], it was hypothesized that the aged rats possessed a decreased metabolic capability. A decreased rate of metabolism would result in an increased duration of action of the compounds administered in the maze experiment, and possibly produce an additive decrement in maze performance in the aged rats. Furthermore, as it is known that both AMI and ZIM possess active metabolites, changes in pharmacokinetic parameters occurring with age would be expected to alter the influence of these metabolites on maze performance in the aged rats as well. The results of kinetic analysis with ZIM showed a significant increase in the elimination half-life in old rats, while in young rats there was a faster rate of formation of norzimelidine, as well as significantly higher levels of this metabolite in plasma at one and two hours following infusion of the drug. If norzimelidine exerts a similar effect on memory as ZIM [2], it is possible that the higher rate of formation of norzimelidine as well as the higher level of this metabolite in young rats may account in part for the apparent increase in maze performance seen in this treatment group as compared to aged rats.

The differences in metabolism of AMI were found to be similar to those of ZIM; in contrast to norzimelidine, however, no significant age-related difference was found in the formation of nortriptyline. The changes in pharmacokinetics of AMI occurring with age would appear to contradict the findings concerning formation of nortriptyline; however, this discrepancy is more apparent than real, as it has been found that nortriptyline is only one of several metabolites formed after *in vivo* administration of AMI [6,7]. As the present results do not clearly indicate the contribution of nortriptyline to the behavior of the rats employed in this study, it remains to be determined what effect, if any, might be exerted by nortriptyline and other metabolites of AMI on memory function. However, in light of evidence that measurement of plasma levels of AMI and nortriptyline may not

necessarily be a reflection of their levels in brain [6,7], the influence of these and other metabolites on memory function may be difficult to determine.

As the present study used only one dose level of the antidepressant compounds, an important question remains as to whether the behavioral effects seen here are dose-related. ZIM has been shown to produce a significant dose-related increase in mean step-through latency in the one trial passive avoidance procedure using Swiss-Webster mice [2], while SCOP has been shown to have opposite effects [13]. The behavioral effect of ZIM on short term memory has been suggested to be due to its ability to prevent the re-uptake of serotonin in the CNS [2], while it has been suggested that SCOP produces a detrimental effect on short term memory by competitive blockade of postsynaptic central cholinergic neurons. The detrimental effects seen with AMI, in conjunction with studies demonstrating its antagonistic properties at the muscarinic cholinergic receptor [14,37], suggests that this drug produces its effect in a manner similar to SCOP, i.e., blockade of postsynaptic central cholinergic neurons. Thus, while larger doses of AMI could be expected to produce a more severe decrement in maze performance, and perhaps at a point in time sooner than that demonstrated in this study, it must be emphasized that higher doses of AMI, which possesses significant anticholinergic potency both peripherally and centrally, have been found to have marked sedating effects in aged rats (unpublished observation). The sedating effect of this compound, especially in aged rats, would most likely preclude the detection of a specific interference with memory.

This study has demonstrated behavioral responses to the administration of compounds with centrally active anticholinergic properties in young and aged Fischer 344 rats. However, a question not addressed in this study is the possible correlation of age-related changes in central muscarinic receptors with changes in maze performance. This question could be addressed by incorporation of receptor binding studies into the present behavioral paradigm. This approach could help clarify the question of whether the changes in behavioral performance seen in the present experiment are related to changes in receptor number, subtype, and/or affinity [29,35].

In conclusion, we believe that the general approach of utilizing behavioral and pharmacokinetic experiments to investigate age-related effects of drugs on memory offers a unique perspective which can be expanded to include other classes of centrally active psychotropic agents and other behavioral paradigms designed to measure specific CNS functions. An approach of this type can be potentially useful in discovering the underlying cause or causes of behavioral drug effects.

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