Behavioural Pharmacology

Etazolate improves performance in a foraging and homing task in aged rats

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ABSTRACT

Etazolate is a phosphodiesterase 4 (PDE4) inhibitor and $GABA_A$ receptor modulator that also stimulates alpha-secretase activity and neurotrophic soluble amyloid precursor protein ($sAPP\alpha$) production, currently developed as a possible Alzheimer's disease therapeutic. In this study two doses of etazolate were tested for cognitive effects in normally aged rats, using a complex spatial learning and memory task that emphasized two naturally occurring behaviors in rodents, foraging for food and returning large pieces of found food to a safe home location. Both etazolate doses completely prevented both (1) a foraging deficit that developed in untreated aged rats over the course of the test, as well as (2) a trial-specific deficit in memory for previously visited food locations that also developed over the course of the test in untreated aged rats. Both doses also significantly reduced a separate memory deficit for changing locations of the animals' home box, plus completely prevented a significant tendency for untreated aged animals to attempt entry into similar-appearing but incorrect home boxes. The combined behavioral data demonstrate positive effects of etazolate on separate age-related cognitive deficits, using a complex task based on naturally occurring rodent behaviors.

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1. Introduction

Among the available animal models usable to examine potential therapies for age-related cognitive impairments, the aged rat has the advantage of being a naturally occurring model, i.e. one without a genetic or lesion manipulation. Such model seems especially appropriate for testing therapeutics that may act via multiple pathways or mechanisms. In the current study, we used aged Fischer–Brown Norway (FBN) rats to examine cognitive effects of etazolate, whose potential for improving age-related cognitive deficits derives from the facts that it (1) enhances the CREB pathway and modulates the $GABA_A$ receptor which are targets for procognitive strategies and (2) stimulates alpha-secretase activity and neurotrophic soluble amyloid precursor protein ($sAPP\alpha$) production and is neuroprotective against beta amyloid peptide via $sAPP\alpha$ (Marcade et al., 2008). An etazolate dependent increase in $sAPP\alpha$ would counteract the reduction in $sAPP\alpha$ that has been correlated with memory loss (Anderson et al., 1999; Fellgiebel et al., 2009). The task we used, a modification of the Barnes maze (Barnes, 1979), termed a Foraging/Homing task, utilizes naturally occurring rodent behavior and so requires minimal specific learning. Pilot studies had shown that aged FBN rats display several distinct deficits in this task, including a persistent inefficient search strategy and a transient short-term spatial memory impairment (Drott and Haun, 2000; Drott et al., submitted for publication).

The Foraging/Homing task is based on natural foraging and hoarding behavior by rodents. The animal chooses a location to search for food, conducts the search, determines whether to consume the food where it is found or bring it to another location for either consumption or hoarding, and if the latter, navigates to either a food storage point or its home location. Current understanding of this complex behavior is focused on optimal foraging theory (for reviews see Stephens and Krebs, 1986; Commons et al., 1987; Shettleworth, 1998) and the neural bases of returning to a home location with found food, where the food is either hoarded or consumed (Whishaw and Tomie, 1989; Whishaw and Gorny, 1999).

Here, food-restricted rats are allowed to search for food pellets placed in 3 of 21 cups on a circular platform, and then return to their home box to either hoard or consume the pellets. The home box is located on the periphery of the circular search area. Over several trials, the rats learn which food cups contain food pellets, and must remember which of 8 identical boxes along the circular periphery is their home box, i.e. the box from which they exited to begin foraging. The food pellets are 1000 mg in size, large enough to produce hoarding behavior in rats (Whishaw and Tomie, 1989). Dependent measures are total number of visits to all food cups during the test, repeat visits to individual food cups during each individual foraging session before successfully finding a food pellet, and length of the return path to the animal's home location. The apparatus used here has also recently been employed to investigate the roles of the vestibular system and the hippocampus in dead reckoning (Wallace et al., 2002; Wallace and Whishaw, 2003).

2. Materials and methods

2.1. Drug preparation

Etazolate (1-ethyl-4-(N′-isopropylidene-hydrazino)-1H-pyrazolo [3,4-b]pyridine-5-carboxylic acid ethyl ester hydrochloride) was synthesized at Pharmasynthese (Lisses, France) and was supplied in powder form in storage vials by ExonHit Therapeutics (Paris, France). The salt/base ratio was 1.126. The drug was prepared in 0.9% saline immediately prior to dosing. All preparations were stored at 4 °C in dark vials shielded from light. Different groups of aged rats received one of two dosages, 0.79 and 2.37 mg/kg. Dosing was by oral gavage in a volume of 0.5 ml/kg and occurred daily, beginning 7 days prior to the start of behavior testing, and continuing daily throughout testing at one hour prior to testing and at equivalent times on non-testing days (weekends). Aged control and Young control animals received an identical dose of saline on the same schedule.

2.2. Animals

The protocol for this study was approved by the Lehigh University Institutional Animal Care and Use Committee, Bethlehem, Pennsylvania, USA, in whose research facilities the study was conducted. Animals used for this study were male Fisher/Brown Norway rats, 28–31 months of age at study initiation, in addition to a control group of 12 young males (9 months of age at study initiation) of the same strain. All animals were obtained from Harlan Industries, Inc (Indianapolis, Indiana, USA). Of the 48 aged rats intended for use in this study, 29 completed the test and all their data analyzed. Six animals were never assigned to a group due to poor appearance (discoloration of fur, low body weight), and 6 died during testing (etazolate 0.79 mg, $n=2$; etazolate 2.37 mg, $n=1$; vehicle control, $n=3$). In addition 7 aged rats that had been assigned to a group and began the habituation phase of the study (prior to behavioral testing), were not tested further because they failed to meet the habituation criterion (see Section 2.4.1 Habituation): etazolate 0.79 mg, $n=3$; etazolate 2.37 mg, $n=1$; vehicle control,. $n=3$.

The animals were housed in pairs in polycarbonate cages lined with Harlan Teklad Contact Bedding in a temperature-controlled room (25 °C) with a 12 h light/dark cycle. Upon arrival, animals were initially provided with water and food (Teklad Global Diet) ad libitum. All animals were weighed prior to the study and the volume of each drug dose (or vehicle) administered was based on the animals' individual body weights. Animals were observed for clinical signs after each dose administration. Prior to testing, animals were initially reduced to 85% of their pre-test weight, and maintained at that level throughout testing, using Teklad Global Diet, 18% protein (Harlan Teklad, Madison, Wisconsin, USA).

2.3. Foraging/Homing apparatus

The testing apparatus consisted of a circular platform (178 cm diameter), with a surface of rough, opaque Plexiglas. Eight identical black boxes, one of which was designated as the animal's home box, surrounded the perimeter of the platform equi-distant from each other. The boxes were constructed of black Plexiglas (23 cm×23 cm×23 cm), enclosed on three sides, with a guillotine door comprising the fourth side; the top was covered with a removable roof. A piece of black felt was placed in front of the guillotine door of each box. In the seven non-home boxes the guillotine door remained down during all trials, while in the home box the (unseen) guillotine door was always in the up position. Twenty-one white plastic food cups were permanently attached to the platform in an irregular pattern. Three of these cups contained one food pellet each (1 g bacon-flavored reward pellets, Bio-Serve, Frenchtown, New Jersey, USA), and while the position of the animal's home box changed throughout testing, the location of the food-containing cups remained constant for each animal. The

location of the food-containing cups was chosen so that the summed straight-line distances between the three cups and the home box varied by less than 3 cm for each of the three home-box locations used for each animal. While this summed distance differed for each animal, it was equivalent when summed over each experimental group of animals. The vertical lip of the cups was high enough so that the animals could not see whether a cup contained food or not without placing their snout inside the cup.

2.4. Procedure

2.4.1. Habituation

Before the task began, the animals were habituated to the apparatus and to the task requirements. Each animal was conveyed from the housing room to the testing room in its residence cage, then taken from its residence cage and placed immediately into the designated home box. The home box contained a small amount of bedding taken from the residence cage. The home box (containing the animal) was affixed to one of the eight possible locations (randomly selected) on the periphery of the circular platform. A large (1000 mg) food pellet was placed in each of the 21 food cups attached to the platform. In addition a pellet was placed directly on the platform just outside, and to one side of, the opening of the home box, with a second pellet placed on the platform slightly further toward the center from the initial pellet. The felt across the opening of the home box was folded back, allowing the animal an unobstructed view of the circular platform from the home box. Each animal then received one 10-minute habituation session each day, during which it exited the home box, retrieved a food pellet, and carried it back to the home box. Each session continued until 3 pellets were retrieved or 10 min had elapsed. After the first session the pellets on the platform (but not those in the food cups) were removed. On subsequent sessions, when the animal began to exit the home box without hesitation, the felt was placed over the entrance to the home box, requiring the animal to push it aside in order to exit the box. If an animal began to eat a pellet without first returning to the home box, it was immediately removed from the platform and returned to its home box. The daily habituation sessions continued until the animal retrieved pellets from 3 food cups and returned them to its home box without attempting to consume them. Any animal that did not meet this criterion after 10 sessions was not tested further.

2.4.2. Home location 1

On the day after meeting the habituation criterion, the animal was again placed in its bedding-containing home box, which was then placed in a new location 90 degrees away from the habituation location. Food pellets were then placed in only 3 selected cups, specific for the particular home-box location (see Foraging/Homing apparatus). No two of these three baited cups were adjacent to each other, nor was any baited cup the closest cup to the home box. The location of the pellets remained constant for each animal throughout the study. The animals then received a single test trial, during which the animal was required to retrieve all three food pellets and return with them to its home box. An incorrect box approach was considered to have occurred if the animal came within 4 cm of any part of a non-home box while carrying a food pellet in its mouth. This incorrect approach was termed an "error" and was recorded as such. A trial was terminated when either (a) all three pellets had been returned to the home box, or (b) 12 min had elapsed. Each animal received 1 trial/day until reaching a criterion of 2 consecutive error-free trials completed within 12 min apiece, up to a maximum of 10 trials.

2.4.3. Home locations 2 and 3

When the animal met criterion for home location 1, the home box was moved to a new location, 135° away from the previous location. Trials continued using the same procedure and criterion as for home

location 1, again up to a maximum of 10 trials. For this second home-box location, the position of the food pellets remained the same as during the first home location; only the location of the home box was moved (see Foraging/Homing apparatus). When criterion for home location 2 was met, the home box was moved once again to a new location, 90° from the previous location. Trials continued using the same procedure as during home location 1. Meeting criterion for home location 3 marked the end of the test.

2.5. Data analysis

Each trial was videotaped from an overhead camera linked to image analysis software (Ethovision 3.1, Noldus Information Technology, Wageningen, Netherlands). Due to large differences in variance between the initial 3 and final 3 pellet retrievals, as well as at the first home box location compared to the subsequent two locations, data was analyzed separately for the initial and final sets of three trials at each home box location (except for the Errors and Trials to Criterion data, which were collapsed over all trials), using separate ANOVAs. Fisher's LSD tests (protected t-tests) were performed when omnibus ANOVA was significant. Standard error of the mean was calculated by dividing the standard deviation by the square root of the sample size minus one. All analyses were performed on a PC-based computer using GB-STAT software (ver.7).

3. Results

3.1. Foraging

In the foraging component of this task, the animals searched for three reward pellets, each of which was placed in one of 21 possible food cups in the search area. The efficiency of this search was measured by counting the number of food cups searched before the animal successfully found and retrieved all three food pellets. The episodic memory component of the animals' search efficiency was measured by counting the number of repeat visits to cups that had already been visited during a single trial.

3.1.1. Total food cups searched

As expected, the aged (vehicle) animals tended to search more food cups overall than young rats before finding the food pellets, and this tendency increased as testing progressed, i.e. as the animals' home box location changed (Fig. 1). However, the difference between young and aged vehicle control animals did not reach statistical significance until the criterion trials at the final location (home location 3), $P<0.005$ following overall ANOVA, F $(3,37)=4.18$, $P<0.02$. This later developing, age-related impairment in search efficiency was prevented by etazolate at both tested doses, $P<0.004$ for 0.79 mg and $P<0.03$ for 2.37 mg. Indeed there was no difference between the aged etazolate-treated animals and young animals.

3.1.2. Repeat visits to food cups

A component of the aged animals' impaired search efficiency was their tendency to make repeat visits to food cups previously visited within the same trial, irrespective of whether those food cups had previously contained food (Fig. 2). Again the aged control animals tended to perform worse than young controls throughout the test, with the impairment becoming severe and significant on the last three retrievals from home location 3, $P<0.0003$ following overall ANOVA, F $(3,37)=7.28$, $P<0.0006$. And again this developing impairment in episodic memory by the aged animals was prevented by etazolate at both tested doses, $P<0.0005$ for 0.79 mg and $P<0.003$ for 2.37 mg, with both these groups of aged animals not different from young controls.
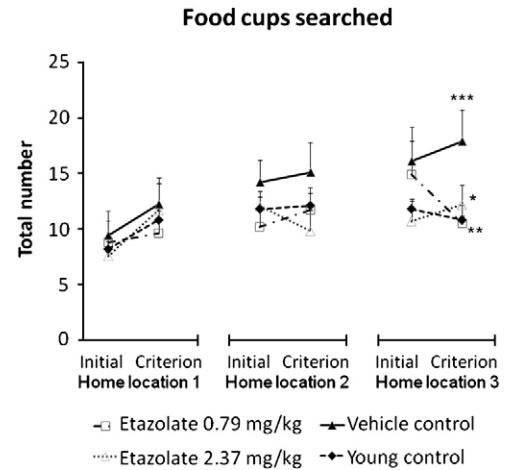

Fig. 1. Total number of food cups searched by young, aged vehicle control, and aged etazolate-treated rats prior to retrieving the initial and final three pellets from different locations of the home box (mean ± S.E.M.). *** = $P<0.005$ vs. Young control, ** = $P<0.004$ etazolate 0.79 mg vs. Vehicle control, * = $P<0.03$ etazolate 2.37 mg vs. Vehicle control.

3.2. Return path distance

In the homing component of this task, each animal returned to its home box after obtaining one of the reward pellets. The animals' memory for the location of their home box (from which they had exited in order to search for food) was assessed by measuring the summed distance taken to return to the home box with all three retrieved food pellets. The aged (vehicle) animals had a significantly longer return path distance than the young animals, i.e. they wandered more, when returning to their home box at Locations 2 and 3 on both initial and criterion trials (P's<0.0002 or less following overall ANOVA's, F $(3,37)=5.47$ or larger, P's<0.004 or less; see Fig. 3). The same was true at location 1 during the first three retrievals, $P<0.0001$ following overall ANOVA, F $(3,37)=P<0.001$.

This deficit in memory for the (changing) home box location was significantly reduced by etazolate at both tested doses on the initial trials at all three home box locations (P's<0.03 or less vs. Vehicle controls). On the criterion trials at all locations, aged animals receiving etazolate at both tested doses were not significantly different from Young controls, with two exceptions: the aged animals
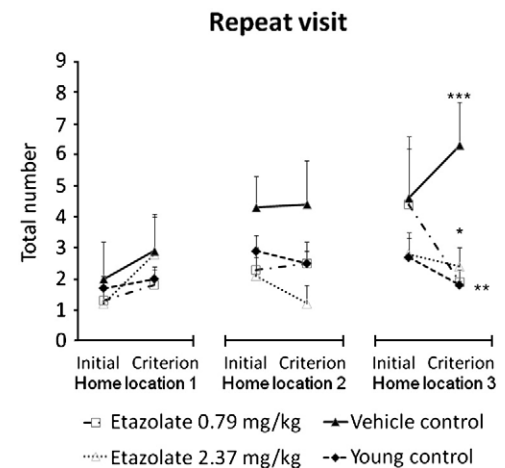

Fig. 2. Total number of repeat visits by young, aged control, and aged etazolate-treated rats to food cups previously visited within the same trial (mean ± S.E.M.). *** = $P<0.0003$ vs. Young control, ** = $P<0.0005$ etazolate 0.79 mg vs. Vehicle control, * = $P<0.03$ etazolate 2.37 mg vs. Vehicle control.
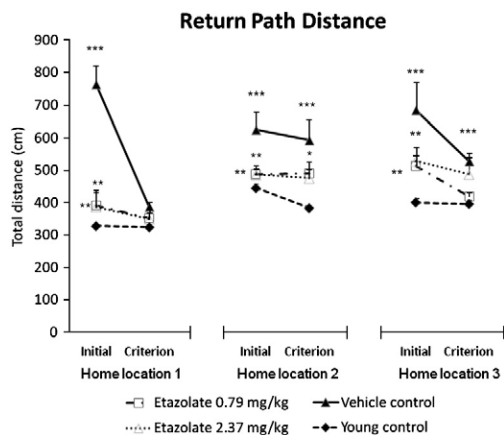
Return Path Distance

Fig. 3. Total distance (cm, mean ± S.E.M.) traversed by young, aged vehicle control, and etazolate-treated aged rats returning to their home box following the initial and last three pellet retrievals when their home box was at three different locations. *** = $P<0.0002$ or less vs. Young control; ** = $P<0.05$ or less vs. Vehicle control; * = $P<0.05$ or less, etazolate 0.79 mg/kg vs. Vehicle control and Young control.

receiving etazolate 0.79 mg/kg took a significantly longer distance to reach their home box than Young controls on the criterion trials at location 2 ($P<0.04$), although not as long as aged Vehicle animals ($P<0.05$); and the aged etazolate 2.37 mg/kg animals took a longer distance at location 3 ($P<0.02$).

3.3. Errors

Aged vehicle control animals made significantly more attempts to enter non-home boxes (errors) when returning with food pellets, compared to young animals, at all three homebox locations (data summed over retrievals, P's<0.0006 or less, following overall ANOVAs, $F(3,37)=5.37$ or greater, P's<0.004 or less; see Fig. 4). All etazolate-treated groups significantly prevented this age effect, at all locations (P's<0.05 or less), and were not significantly different from each other or Young controls in this measure of homing accuracy (with the single exception of etazolate 0.79 mg at the third home box location, where this group was significantly worse than Young control animals, $P<0.02$).
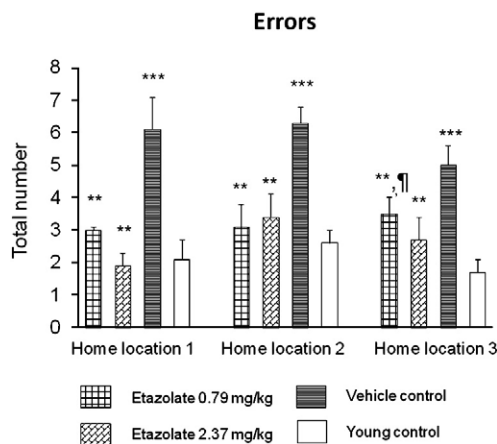
3.4. Trials to criterion

At the start of this test (location 1), the aged vehicle controls required significantly more trials to reach criterion than the young animals ($P<0.00001$ following overall ANOVA, $F(3,37)=11.21$, $P<0.00003$). Etazolate 2.37 mg/kg prevented this deficit, i.e. this group required significantly fewer trials than the vehicle group ($P<0.002$) and was not significantly different from the young group (Fig. 5). The aged vehicle animals quickly improved in this measure, and were not significantly different from young animals at Locations 2 and 3.

4. Discussion

The Foraging/Homing task used here employed five different measures of cognitive performance, and on all of these measures aged rats treated with 2.37 mg/kg etazolate performed consistently better than aged vehicle controls, often performing no differently from young controls, while aged rats treated with the lower dose (0.79 mg/kg) displayed improved performance less consistently on four of the measures.

4.1. The Foraging/Homing task

This task uses two naturally occurring behaviors of rodents, foraging and returning to a safe location to either eat or store (hoard) a large, found food item. The return-to-a-safe location aspect ("homing") is based on the Barnes maze (Barnes, 1979), a dry-land version of the classic water maze used to assess spatial memory in rodents. Whishaw et al. have modified the task to investigate the neural mechanisms underlying navigation to the home box (Maaswinkel and Whishaw, 1999; Whishaw, 1998; Whishaw and Gorny, 1999; Whishaw and Maaswinkel, 1998; Whishaw and Tomie, 1997), but their modifications do not include the multi-site food locations used here.

Spatial learning and memory deficits in aged rats are well documented (e.g. Gage et al., 1988; Lindner, 1997; Lindner and Schallert, 1988), so it is not surprising that the aged vehicle control rats in this study were impaired in returning to their home box location, a deficit seen on the initial trials from each of the three home box locations. The aged controls were able to learn over time however, requiring less distance to reach their home box on the final (criterion) trials, to the point that they moved in a virtually straight line from the pellet-containing cups to the home box at location 1, as did the young controls. When the home box was moved to two different locations, spatial learning over time was weaker in aged controls, i.e. their return path
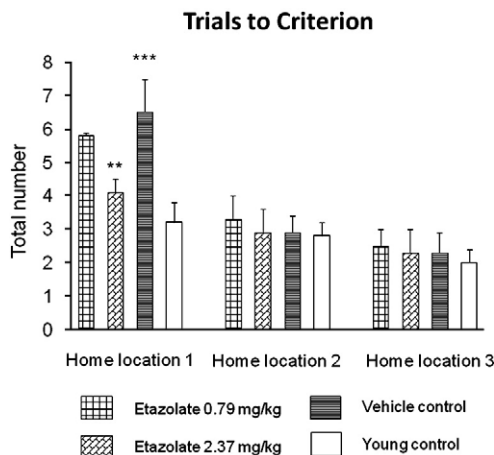
Errors

Fig. 4. Total number of errors committed (mean ± S.E.M.) by young, aged vehicle control, and etazolate-treated aged rats, combined over all retrievals from each home box location. Errors are defined as approaches to non-home boxes following pellet retrieval. *** = $P<0.0006$ or less vs. Young control; ** = $P<0.05$ or less vs. Vehicle control; ¶ = $P<0.02$ vs. Young control.

Trials to Criterion

Fig. 5. Number of trials (mean ± S.E.M.) needed to reach criterion for returning accurately to each home box location, by young, aged vehicle control, and etazolate-treated aged rats. *** = $P<.0001$ vs. Young controls; ** = $P<.002$ vs. Vehicle controls.

distance remained significantly greater than young controls, possibly because the animals remained on the table longer searching for the food pellets (see below) and their memory for the new spatial location of the home box became weaker. Nonetheless this task is able to distinguish between an initial spatial memory deficit and spatial learning. The second measure of spatial memory in this task is return errors. On this measure, aged controls are consistently impaired relative to young controls across all home box locations. Thus this task can also distinguish between a transient spatial memory deficit and a persisting one.

The unusual aspect of this task is the addition of a foraging component. The animals must find 3 large-size reward pellets placed among 21 possible food cups. Their large size motivates the homing component (above). While previous foraging research has mostly utilized birds (e.g., Stephens and Krebs, 1986), the present study suggests that this naturalistic function may be useful for age-related cognitive deficits. Indeed, the most consistent age effect seen here was reduced efficiency in foraging by aged rats. A related impairment in the aged controls was significantly increased numbers of repeat visits to food cups, within the 12-minute trials. However this deficit occurred only at the second and third home box locations, where foraging efficiency also worsened for the aged controls. Qualitatively, the old animals did not appear to be searching randomly for the food pellets; rather, they tended to confine their search regions to areas covering about one-third of the platform surface, as did the young animals. However the old animals did not search as efficiently as the young animals, visiting a significantly greater number of cups on the platform before retrieving a reward pellet and they tended to get worse with practice. Since in the same task the old animals did learn spatial information (see above), their inefficient foraging appears to reflect more than a memory deficit, if indeed it reflects any memory deficit at all. This search strategy, refractory to practice, seems akin to the disorientation in dementia (American Psychiatric Association [DSM-IV-TR], 2000; Lai and Arthur, 2003; Monacelli et al., 2003; Rowe and Glover, 2001), even frontotemporal dementia (Hornberger et al., 2008).

The aged rats' impaired search strategy may also result from an olfactory deficit. However, Kraemer and Apfelbach (2004) showed no difference in rat olfactory discrimination and olfactory cognitive abilities with age. Schoenbaum et al. (2002) also showed that aged rats are not impaired in an initial discrimination task but while being significantly slower in learning a reversal task based upon previously paired odors, eventually do learn the task. Given that the reward pellets never changed locations throughout the entire task, it seems unlikely that the inefficient search strategy displayed by the aged animals would be based upon olfaction, as at least some improvement might be expected here.

4.2. Effects of etazolate

Both doses of etazolate significantly lessened (and at home location 1 completely prevented) the aged animals' initial impairment in learning the home box locations. At locations 2 and 3, where aged controls animals remained impaired at the end of the learning period (criterion trials), both doses significantly lessened this learning deficit at location 2 while the lowest dose did so at location 3. In the other measure of spatial learning – visits to incorrect home boxes (errors) – both doses significantly improved home accuracy at all three locations, with the higher dose completely preventing this deficit. Thus in aged rats, etazolate improved both initial memory for a spatial location, learning of new spatial locations over time, and accuracy of spatial memory.

In the foraging component of this task, both doses of etazolate completely prevented the significant worsening of search efficiency over repeated testing displayed by aged controls, as etazolate-treated old rats searched as few food cups as young rats before successfully finding the reward pellets. These two doses also completely prevented development of a significant impairment in episodic memory that

otherwise occurred in aged vehicle animals, an increase in repeat visits to food cups previously visited within the 12 min trials. Again the etazolate-treated old animals' memory for recently visited food cups was as good as the young animals.

Etazolate may prevent a growing impairment in foraging efficiency by aged animals, or rather alter their cognitive strategy. Specifically, as the task progressed, all aged groups required fewer trials to reach criterion from the first to the last home box location and also tended to spend more time searching between successful retrievals as the test progressed. The aged controls also appeared to use a trail-following search strategy, retracing their previous search area within a trial before moving on to another search area. This apparent strategy coupled with the additional search time meant the aged controls had more opportunity to search more (empty) food cups before successfully finding a pellet. In contrast, etazolate-treated groups appeared to adopt a search strategy similar to that employed by young controls: after a pellet was retrieved, the search area for the next pellet was different. Thus the etazolate groups became more efficient in their search strategy, an improvement especially noticeable for repeat-visits-to-food-cups. Regardless of the interpretation, aged controls demonstrated an increased impairment in both foraging measures throughout the test, and both doses of etazolate prevented this impairment by the end of the test.

There is some dissociation between the foraging and homing measures on this task. With increasing trials at each home box location, aged controls improved on the return path distance measure but declined on both foraging measures, indicating that these measures reflect separate cognitive processes. Additionally, the two homing measures (return path distance, and errors) appear to reflect different cognitive processes: aged controls made significantly more attempts to enter non-home boxes (errors) when returning with reward pellets, at all three homebox locations, and this impairment remained constant during the test. In contrast aged controls were able to decrease their return path distance over the course of this test. The ability of etazolate both to shorten return path distance and to reduce approaches to incorrect home boxes, and prevent development of an impairment in foraging efficiency, thus indicates that etazolate is positively affecting different age-related cognitive impairments.

This work is the first report of a procognitive effect of etazolate, whose positive effects in multiple measures of this complex task in aged rats strongly suggest a potentially useful role in treating dementia conditions, such as Alzheimer's disease. Etazolate also counters the effect of scopolamine on novel object recognition in adult rats (our unpublished observations). These multiple positive effects suggest that etazolate may be acting through multiple pathways which may involve the CREB pathway and GABA$_A$ signaling for neuroplasticity, learning and memory (Xia et al., 2009). A possible route of action of etazolate is its effects on alpha-secretase and procognitive sAPPα production (Marcade et al., 2008) which is reduced in Alzheimer's disease and aging (Lannfelt et al., 1995; Nistor et al., 2007; Fellgiebel et al., 2009). Finally, preclinical neuroprotection and cognition studies as well as pharmacokinetic and safety profiles in Phase I and Phase IIa clinical studies have established that etazolate is a well-tolerated drug devoid of major side effects which may offer novel disease modifying and symptomatic therapeutic potential for the treatment of Alzheimer's disease.

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