Effects of Benzodiazepine Receptor Inverse Agonists and Nicotine on Behavioral Vigilance in Senescent Rats

Janita Turchi, Lee Ann Holley, and Martin Sarter

Department of Psychology and Neuroscience Program, The Ohio State University, Columbus.

AGING is associated with impairments in various cognitive functions, specifically in attentional processes (e.g., Parasuraman et al., 1989; Greenwood and Parasuraman, 1991; Parasuraman and Giambra, 1991; Greenwood et al., 1993). Efforts to develop pharmacological strategies for the treatment of age-related cognitive impairments have been impeded by considerable difficulties in the development of animal procedures to test attentional functions and to model the age-related impairments in these functions in animals, particularly rodents (Moore et al., 1992a; McGaughy et al., 1994; McGaughy and Sarter, 1995b).

Using a recently developed and validated procedure for the assessment of behavioral vigilance in rats (Bushnell et al., 1994; McGaughy and Sarter, 1995a), we demonstrated that, compared with 6-month-old BNNia/F344 rats, the performance of 20-month-old rats in a behavioral vigilance task was significantly impaired. Specifically, 20-month-old animals failed to detect shorter signals, while the detection of longer signals remained unaffected. Age did not affect the animals' ability to reject correctly the absence of signals, the number of omissions, or side bias. The profoundly detrimental effects of the benzodiazepine receptor (BZR) agonist chlordiazepoxide interacted with the effects of age, signal length, and time on task. These data correspond with the increased potency of BZR agonists to impair cognitive functions in aged humans (e.g., Pomara et al., 1989; Nakaido et al., 1990) and were speculated to reflect an interaction between the age-related changes in the basal forebrain cholinergic system (e.g., Meyer et al., 1984; Altavista et al., 1990; Armstrong et al., 1993) and the effects of BZR agonists on task-associated activation of this system (Sarter and Bruno, 1994; Sarter et al., in press). Because negative modulators of GABAergic transmission were previously shown to potentiate activated acetylcholine (ACh) efflux (e.g., Moore et al., 1993, 1995; Sarter and Bruno, 1994), these compounds were expected to attenuate the effects of age on vigilance performance. However, the BZR weak inverse agonists ZK 93 426 and 3-CCTB failed to affect vigilance performance, and the partial inverse agonist RU 33965 actually impaired performance in both 6- and 20-month-old animals (McGaughy and Sarter, 1995a).

It was speculated that BZR inverse agonists may have failed to produce beneficial effects on the performance of 20-month-old rats because these animals' performance, while significantly different from younger rats, was not sufficiently impaired to allow a robust beneficial drug effect. Furthermore, age-related changes in the cholinergic system were typically demonstrated in animals older than 20 months (Strong et al., 1980; Altavista et al., 1990; Armstrong et al., 1993). As beneficial behavioral effects of BZR inverse agonists were found in animals and humans with impaired cholinergic systems (Jensen et al., 1986; Lorez et al., 1988; Sarter et al., 1988; Hodges et al., 1989; Sarter and Steckler, 1989; Deacon et al., 1990; Holley et al., 1992; Mazurkiewicz et al., 1992; Duka et al., 1993; for review, see Sarter et al., 1994), such effects were expected in sufficiently aged animals that show morphological and functional decline in the forebrain cholinergic system. Thus, in the present experiment, the effects of ZK 93 426 (Braestrup et al., 1984; Jensen et al., 1984; Sarter et al., 1994) and RU 33965 (Deacon et al., 1990; Gardner et al., 1993) on the performance of older rats, aged 28 months (see Coleman et al., 1990), were tested. Additionally, the effects of nicotine were examined because the acute administration of this compound did not produce any effect on the performance of 6-month-old rats in this task (Turchi et al., 1995) but was reported to produce beneficial...
effects in aged animals or in animals with cholinergic dysfunctions (Buccafusco and Jackson, 1991; Muir et al., 1995; for review, see Levin, 1992).

METHODS

Subjects. — Male BN/Nia/F344 rats (National Institute on Aging Colony, Charles River Breeding Laboratories, Stoneridge, NY), aged 22 months at the commencement of behavioral training, and aged 27.8 ± 1.09 months (Mean ± SEM) at the beginning of drug testing, were housed individually in a light- (12 h light/12 h dark, on 0600 h) and humidity-controlled room. Animals were moderately food deprived (maintained at 90% predeprivation weight), and water was available ad libitum. The experiment started with eight animals, five of which received all treatments; one animal did not recover from a respiratory disease, and two animals never approached stable, above-chance baseline performance. The experiment was conducted in AAALAC-accredited facilities and in accordance with the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training."

Apparatus. — Operant chambers (MedAssociates, East Fairfield, VT) equipped with two retractable levers, a house light (2.8 W), a food dispenser, a 2900 Hz sonalert, and three panel lights (2.8 W each) were employed. The food dispenser was located such that animals were required to turn away from the intelligence panel to obtain reinforcement. Signal presentation, lever operation, and food pellet (Noyes pellets, 45 mg) delivery were controlled by an IBM 386 clone and Med-PC software (MedAssociates). A Tenma Digital Lumeter (model 72-580, accuracy of ±0.5% for 6.28 × 10⁻³ cd/cm² and ±2% repeatability) was employed to assess the luminance of the various signals (see below). The stimulus lights were 12.7 cm high on the intelligence panel. The Lumeter (6.35 cm high), placed 17.78 cm away from the intelligence panel facing the stimulus lights, measured the luminance of the chamber with house light and stimulus lights off at 3.14 × 10⁻³ cd/cm² and with house light only at 1.07 × 10⁻³ cd/cm². The luminance of the three stimulus possibilities (presented by means of the center panel light), with house light on, was as follows: 500 msec: 6.09 × 10⁻³ cd/cm²; 50 msec: 1.71 × 10⁻³ cd/cm²; 25 msec: 1.37 × 10⁻³ cd/cm².

Procedure. — Animals were trained between 1600 and 1800 h daily. The vigilance task and training procedures are described in detail in McGaughy and Sarter (1995a). Briefly, animals were first trained to bar press using a fixed ratio (FR1)-schedule of reinforcement. Animals were then trained to discriminate between signals (central panel light illumination for 1 sec) and nonsignals (no illumination). Two seconds following signal or nonsignal, the levers were extended and remained active for 4 sec. A left lever press following a signal was counted as a hit and rewarded. During this trial type, right lever presses were counted as misses and were not rewarded. A right lever press following a nonsignal was recorded as a correct rejection and reinforced. Conversely, in the nonsignal situation, left lever presses constituted false alarms and were not reinforced. Intertrial intervals (ITI) lasted 12 ± 3 sec. At this stage of training, misses and false alarms resulted in correction trials in which the previous trial was repeated. Following three incorrect responses to repeated correction trials, a "forced" correction trial occurred during which only the hit-or correct-rejection lever (depending on the trial type) was extended. During forced correction trials, the lever remained active for 90 sec and the (non-)signal was also presented for 90 sec. Forced correction trials counteracted the development of side biases. Once the animals performed >59% hits and correct rejections for a minimum of three consecutive sessions, correction trials and forced correction trials were eliminated and the length of the signal was varied (25, 50, or 500 msec). Of the 162 trials per session, 27 trials of each of the three signal lengths were presented (yielding a total of 81 signal trials). The remaining 81 trials were nonsignal trials. As it was planned to analyze the effects of prolonged performance in this task, the total number of trials was divided into three blocks of 54 trials; the sequence of signal and nonsignal trials was randomized such that the following parameters were met: each block consisted of 9 trials per signal length and 27 nonsignal trials (see McGaughy and Sarter, 1995a). Finally, the ITI was reduced to 9 ± 3 sec in an attempt to achieve a vigilance decrement for shorter signals (Holley et al., 1995; McGaughy and Sarter, 1995a; Turchi et al., 1995). Animals were trained until they reached asymptotic, stable performance.

Drugs and drug administration. — The sequence of the administration of drugs and doses was counterbalanced across all treated animals. Successive drug sessions were separated by a minimum of two vehicle sessions during which time the animals performed at baseline levels. (−)-Nicotine diol (+) tartrate salt (Sigma, St. Louis, MO; 0.09, 0.287, 0.689 mg/kg in saline; i.p.) was administered 15 min presession. The BZR weak inverse agonist, ZK 93 426 [Schering AG, Berlin, Germany; 0.39, 1.56, 6.25 mg/kg/ml in 10% (wt/vol) solution of Cremophor EL (CEL); polyethoxylated castor oil (BASF, Ludwigshafen, Germany) in saline; i.p.] was administered 20 min presession. RU 33965, a BZR partial inverse agonist (Roussel Laboratories, Swindon, U.K.; 0.1, 0.5 mg/kg/ml in CEL; i.p.), was also administered 20 min presession.

Measures of performance. — From each test session, the number of hits, misses, correct rejections, false alarms, and errors of omissions were recorded. The relative number of hits (h; h = hits/hits + misses) was calculated for each signal length. Furthermore, the relative number of correct rejections (cr; cr = correct rejections/correct rejections + false alarms) was computed for each block of 54 trials. To collapse the performance in signal and nonsignal trials into a single value, a vigilance index (VI) was calculated by adapting the formula for sensitivity index (SI; Frey and Colliver, 1973; Sahgal, 1987; see also Craig, 1987). As pointed out in McGaughy and Sarter (1995a), this index was termed VI to emphasize the differences between the derivation of SI and VI. VI indicates the subject’s ability to discriminate between signals and nonsignals [VI = (h–f)/(2 * (h + f) – (h + f)²); h, relative number of hits; f, relative
number of false alarms]. This index was calculated on the basis of the relative numbers of hits and false alarms (and not on the overall probability for a hit and a false alarm as deduced from signal detection theory. as proposed by Frey and Collier, 1973) to yield VI values that were not confounded by errors of omission. The values for VI vary from –1 to +1. A value of zero indicates the complete inability of a subject to distinguish between signal and nonsignal, and +1 indicates that all responses to signals were hits and all responses to nonsignals were correct rejections. As the effects of different signal lengths (25, 50, 500 msec) were tested in the present experiment, VI values for all three signal types were calculated (VI25; VI50; VI500). In addition to VI and the relative number of hits and correct rejections, the number of errors of omission as well as the side bias (SB) measure were calculated. SB was estimated by dividing the sum of the number of hits and false alarms by the total number of responses. This index varies between 0 and 1, with 1 indicating that all responses were to the hit/false alarm lever, 0 indicating that all responses were to the miss/correct rejection lever, and 0.5 indicating the absence of a side bias.

Statistical analyses. — The effects of the different drugs were analyzed independently. The effects of dose (within-subject variable), signal length (within-subject variable), and block of trials (within-subject variable) were analyzed for each drug using repeated-measures analysis of variance (ANOVA). Significant drug effects on VI were further scrutinized by analyzing effects on the relative number of hits and correct rejections. Percentage data were transformed using the formula \[2 \arcsin (\sqrt{x})\] as described in Zar (1974) in an attempt to normalize the distribution of data. The absolute number of errors of omission as well as the side bias measure were analyzed using repeated-measures ANOVA (with dose x block). To ascertain the locus of main effects of stimulus length, dose, or time during the session (block), Tukey’s honestly significant different (HSD) post-hoc test (\(\alpha = .05\)) was employed. Due to the low number of subjects, various methods to reduce the risk of Type II errors, such as increasing sample size, decreasing variability, or increasing the rejection region, were considered; these were deemed not feasible, either for lack of applicability or the increased risk of Type I errors. Also, given that the direction of the effects of drug administration could not be predicted, one-tailed tests would not have been appropriate. Application of a Monte Carlo analysis also appeared inappropriate because of its assumption of uniformity of variance. Thus, it appeared most reasonable to establish Type I errors (\(\alpha = .05\)) and accept the risk of any consequent Type II errors. Statistical analyses were conducted using the SPSS-PC +5.0.1. software (SPSS Inc., Chicago).

RESULTS

Baseline performance. — Data from each animal’s vehicle sessions from the days before the testing of each dose were collapsed for baseline performance analysis. The animals’ ability to discriminate signal and nonsignal events (VI) was signal length dependent \(F(2,8) = 44.86; \ p < .001\); VI (Mean ± SEM): VI500 = .34 ± .04; VI50 = .15 ± .04; VI25 = .11 ± .02). The effects of signal length on VI were due to a similar effect of signal length on the relative number of hits \(h; F(2,8) = 41.77; \ p < .001; \ h_{50} = 71 ± 3\%; \ h_{50} = 57 ± 3\%; \ h_{25} = 50 ± 2\%; \) note that the relative number of hits theoretically can approach \(h = 0\) (see McGaughy and Sarter, 1995a; Holley et al., 1995); note also that percentage values are given for illustration and transformed values were used for statistical analyses]. Post-hoc analyses failed to reveal the significant differences between the VI values (all \(p > .05\)). However, significant differences between the relative number of hits to the 500-msec signals and the 25-msec signals (HSD = .44; \(p < .05\)) were detected. In addition, time, as revealed by block analysis, significantly affected VI \(F(2,8) = 8.46; \ p < .05\); the locus of this effect was not identified (all \(p > .05\)). The effects of VI were not based on an effect on the relative number of hits \(h; F(2,8) = 1.14; \ p > .05\) but on a time-dependent decrease in the relative number of correct rejections \(r; F(2,8) = 4.47; \ p < .05\); for block 1: 65 ± 3%; block 2: 57 ± 2%; block 3: 52 ± 3%. Post-hoc analyses did not detect which blocks significantly differed (all \(p > .05\)). The number of errors of omission was affected by block \(F(2,8) = 4.49; \ p < .05\), ranging from an omission rate of 4.79 ± 53 trials in block 1 to 7.71 ± 2.13 in block 3 (HSD = 7.62, all \(p > .05\)).

ZK 93 426. — Administration of ZK 93 426 did not affect VI \(F(3,12) = 1.59; \ p = .24\), and the relative number of hits \(F(3,12) = .89; \ p = .47\), correct rejections \(F(3,12) = .42; \ p = .74\), or side bias \(F(3,12) = .53; \ p = .67\). However, the effects of ZK 93 426 and block on VI interacted significantly \(F(6,24) = 2.60; \ p < .05\). This interaction was based on an analogous interaction in the relative number of hits \(F(6,24) = 3.09; \ p < .05\). One-way ANOVAs revealed an effect of block on the relative number of hits only for the highest dose of ZK 93 426 (6.25 mg/kg; \(F(2,8) = 4.68; \ p < .05\)), which accounted for the relatively small number of hits during blocks 1 and 2 following this dose of ZK 93 426. In block 3, the relative number of hits was similar to saline-treated animals (Figure 1). The effects of ZK 93 426, signal length, and block on the relative number of hits did not interact \(F(12,48) = 1.09; \ p = .39\). Similar to previous reports using younger rats (Andrews et al., 1992; McGaughy and Sarter, 1995a), ZK 93 426 increased the number of errors of omission \(r; F(3,12) = 4.45; \ p < .05\); vehicle: 6.27 ± 1.53 omissions/session; .39 mg/kg: 8.27 ± 3.57; 1.56 mg/kg: 8.80 ± 2.91; 6.25 mg/kg: 15.20 ± 4.63. Thus, the available data provide no evidence, not even trends, in support of the hypotheses that ZK 93 426 benefits the performance of aged animals in this task.

RU 33965. — In the analysis of the effects of the BZR partial inverse agonist RU 33965 on VI and the relative number of hits and correct rejections, the data from block 3 of 54 trials were omitted from the final analysis because the high number of omissions precluded a meaningful calculation of the relative number of hits per signal length in some animals. Administration of RU 33965 impaired the ability of the animals to discriminate signal from nonsignal events [VI;
Figure 1. Interactions between the effects of ZK 93 426 and time (i.e., block) on the relative number of hits. This and other graphs show the transformed percent values that were also used for the statistical analyses. To improve the usefulness of these figures, the ordinate also shows percent values (%) assigned to appropriate transformed values. The error bar shows 2 standard errors of the differences between the means and was derived from the dose x block interactions in the analysis of variance. The standard error for the difference between the means for this interaction was computed by deriving the standard deviation (which is determined by taking the square root of the sum of squares for the error term divided by the degrees of freedom) and dividing this value by the square root of the number of mean comparisons. The interaction between the effects of ZK 93 426 and time was a result of the comparatively low relative number of hits during blocks 1 and 2 following the administration of the highest dose of ZK 93 426. Following this dose, the relative number of hits returned to normal levels during block 3.

\[ F(2,8) = 11.26; p < .05 \]. The effects of the two doses did not differ from each other (HSD = .36; \( p > .05 \)). The effects of dose and signal length on VI showed a trend \[ F(4,16) = 2.99; p = .051 \] that reflected a greater decrease in VI following administration of the higher dose of RU 33965 and in response to longest signals than following the smaller dose of RU 33965 or in response to shorter signals. The effects of RU 33965 did not interact with block, and the effects of these two factors did not interact with stimulus length \[ \text{dose} \times \text{block}: F(2,8) = 1.10; p = .37; \text{dose} \times \text{block} \times \text{signal length}: F(4,16) = 1.76; p = .19 \].

The dose effect of RU 33965 on VI was based on effects on both the relative number of hits \[ F(2,8) = 14.56; p < .01 \] and the relative number of correct rejections \[ F(2,8) = 7.84; p < .05 \]. RU 33965 dose-dependently decreased the relative number of hits (vehicle: 62 ± 4%; 0.1 mg/kg: 53 ± 3%; 0.5 mg/kg: 40 ± 5%). The effects of RU 33965 on the relative number of hits interacted significantly with signal length \[ F(4,16) = 3.20; p < .05 \]; see Figure 2]. One-way ANOVAs revealed significant effects of signal length in the effects of vehicle and the lower, but not the higher, dose of RU 33965, reflecting the finding that the detrimental effects of the high dose were signal length-independent. The effects of RU 33965 on the relative number of correct rejections were a result of a decrease in correct rejections following the lower dose of RU 33965 as compared with the higher dose (vehicle: 62 ± 3%; 0.1 mg/kg: 50 ± 4%; 0.5 mg/kg: 67 ± 4%; low versus high: HSD = .36; \( p < .05 \)). The higher dose of RU 33965 shifted the animals' side bias toward the miss/correct rejection lever \[ F(2,8) = 10.59; p < .01 \]; saline: 50 ± .01; 0.1 mg/kg: 52 ± 0.2; 0.5 mg/kg: 37 ± .04 \]. Note that the dose that increased the number of false alarms did not affect side bias. RU 33965 did not significantly affect the number of errors of omission \[ F(2,8) = 4.17; p = .057 \]; note the trend for an increase in omissions following the administration of RU 33965; vehicle: 4.77 ± .81 omission; 0.1 mg/kg: 11.53 ± 5.06; 0.5 mg/kg: 22.07 ± 5.25]. In summary, RU 33965 impaired the animals' performance, and evidence for putative beneficial effects on performance clearly is unavailable.

Nicotine. — Administration of nicotine produced no significant effects (all \( p > .05 \)). However, several trends \( p < .10 \) were further explored to substantiate the conclusion that the rejection of the hypothesis that nicotine produces beneficial effects in senescent animals was not limited by the possibility of Type II errors. There were trends for nicotine to affect VI \[ F(3,12) = 2.92; p = .08 \] and to interact with the effects of signal length on VI \[ F(6,24) = 2.12; p = .09 \]. However, Figure 3 illustrates that these trends did not reflect...
crease VI and, following the highest dose of nicotine, the trend for the relative number of hits \( F(6,24) = 2.00; p = .11 \), although it is unclear; generally, however, they do not indicate beneficial effects of nicotine on performance in this task. The basis for this trend, also reflected in the relative number of hits, is unknown. It is evident, however, the administration of nicotine in 28-month-old animals did not produce beneficial effects on performance in this task.

The relatively poor ability of 28-month-old rats to reject signals and signals in 25-msec. signals appeared smaller than following the smaller doses. The bases for these trends are unclear; generally, however, they do not indicate beneficial effects on performance. These insignificant effects of nicotine on VI clearly were unrelated to the animals' ability to correctly reject nonsignal trials \( F(3,12) = .35; p = .79 \). The trend for an interaction between the effects of nicotine and signal length was also revealed in the analysis of the relative number of hits \( F(6,24) = 2.00; p = .11 \), and there was also a trend for an interaction between the effects of nicotine, signal length, and block \( F(12,48) = 1.69; p = .1 \). Inspection of these data suggested that this trend is a result of dose- and stimulus-dependent recoveries from the initial (i.e., block 1) decreases in the relative number of hits. Again, these data provide no evidence for beneficial effects of nicotine on performance in this task.

**DISCUSSION**

The data from the present experiment demonstrate that administration of the BZR weak inverse agonist ZK 93 426, the BZR partial inverse agonist RU 33965, and nicotine did not produce beneficial behavioral effects on the performance of 28-month-old rats in a behavioral vigilance task. In contrast, all significant effects produced by RU 33965 and ZK 93 426, as well as the trends found in the analysis of the effects of nicotine, pointed to drug-induced impairments in performance. Thus, the present data reject the original hypothesis that these compounds produce beneficial effects on the performance of senescent animals in a behavioral vigilance task. Furthermore, examination of the data does not support the possibility that this hypothesis is falsely rejected, as an increase in the \( \alpha \)-level would favor the detection of drug-induced impairments in performance.

Given that the original hypothesis was based on the notion that lower performance in senescent animals would allow beneficial drug effects to be demonstrated, the possibility that the group of senescent animals that completed the drug regimen was a result of a behavioral selection process that violated the original assumption underlying this experiment needs to be considered. As described in the Results, the performance of these animals was stable, albeit relatively low. Compared with the 20-month-old rats tested previously with a similar environment and procedure (McGaughy and Sarter, 1995a), baseline performance of the 28-month-old rats was clearly further impaired (post hoc comparisons revealed significant effect of old age on VI \( F(1,9) = 9.51; p < .05 \) that did not interact with signal length \( F(2,18) = 3.28; p > .05 \)). However, based on the previous finding that the performance of 20-month-old rats differed from 6-month-old rats primarily by a decrease in the relative number of hits but not in their ability to correctly reject nonsignal trials (McGaughy and Sarter, 1995a), it was expected that the performance of 28-month-old animals would be characterized by a further decrease in the relative number of hits. Such a finding would theoretically correspond with hypotheses about the role of cortical ACh in stimulus detection and processing (Muir et al., 1994; Voytko et al., 1994; Sarter et al., in press), with the effects of 192 IgG-saporin-induced lesions on performance in this task (McGaughy et al., in press) and with the effects of age on the cholinergic system (Strong et al., 1980; Meyer et al., 1984; Altavista et al., 1990; Armstrong et al., 1993). Yet, the decreased overall performance of the animals in the present experiment was not due to a further decrease in the animals' ability to detect signals \( F(1,9) = .35; p > .05 \); rather, it was due to a decrease in the relative number of correct rejections \( F(1,9) = 18.78; p < .01 \). Note that this difference was not merely due to the development of a side bias, as this would have corresponded to a decrease in correct responding to signals. Thus, while the 28-month-old animals' performance was sufficiently low to allow beneficial drug effects to occur, the nature of their performance may have precluded such effects.

BZR agonists were previously found to further decrease the ability to detect signals in 20-month-old animals (McGaughy and Sarter, 1995a). Based on their effects on cortical ACh (see below), the putative beneficial effects of BZR inverse agonists have been assumed to be mediated via attenuation of impairments in performance in signal trials. Indeed, inverse agonist-induced increases in the relative number of hits were observed in animals with 192 IgG-saporin-induced cholinergic lesions of the basal forebrain (McGaughy et al., in press). However, as the performance of 28-month-old animals was not characterized by an augmented decrease in the ability to detect signals, the failure of ZK 93 426 and RU 33965 to produce beneficial effects corresponded to the absence of beneficial effects of these drugs in younger animals (McGaughy and Sarter, 1995a).
ject correctly the absence of signals was unexpected, based on the hypothesis that the effects of age in such a task are mediated via the cholinergic system. In general terms, cortical cholinergic activity has been hypothesized to mediate the enhanced processing of significant stimuli (for review, see Sarter et al., 1995). In support of this hypothesis, 192 IgG-saporin-induced basal forebrain lesions were found to decrease primarily the ability of animals to detect visual signals (McGaughy and Sarter, 1995a). Given these data and the hypothesis that the ability to reject correctly the absence of signals depends less critically on the integrity of cortical cholinergic afferents than the ability to detect signals, it seems unlikely that the 28-month-old animals suffered from a substantial decline in cortical cholinergic function. It is important to note in this context that, while morphological, in vitro and ex vivo measures of cortical ACh indicated age-related impairments in the cholinergic system (Strong et al., 1980; Meyer et al., 1984; Altavista et al., 1990; Armstrong et al., 1993), in vivo measures of ACh efflux did not (Fischer et al., 1991; Moore et al., 1992b, in press). This conclusion is supported by the measurement of cortical ACh release in two of the 28-month-old animals after completion of this experiment; using the microdialysis method described by Moore and colleagues (1993, 1995), baseline frontoparietal ACh efflux in these two animals were found to be .33 pmol/min and .42 pmol/min, respectively, i.e., well in the range of the baseline release of younger animals (Moore, Sarter, Bruno, unpublished observations). Thus, the functional effects of aging in rats on cortical ACh remain unsettled.

Therefore, the bases for the original assumption that BZR inverse agonists should attenuate the relatively low performance of senescent animals in this task were found inaccurate. Furthermore, the conclusion that these compounds do not benefit the attentional performance of senescent animals is not in conflict with the beneficial effects of these drugs in subjects with experimentally induced dysfunctions of the cholinergic system (Jensen et al., 1986; Sarter et al., 1988; Stephens and Sarter, 1988; Hodges et al., 1989; Sarter and Steckler, 1989; Deacon et al., 1990; Mazurkiewicz et al., 1992; Pratker et al., 1992; Turner et al., 1992; Holley et al., 1993; for a review, see Sarter et al., 1994). The present data suggest that senescent animals do not model the impairments in cholinergic functioning that result from lesions or muscarinic receptor blockade. These experimental manipulations produce impairments in attention that are not reproduced in senescent animals; hence, compounds found to benefit the performance of scopolamine-treated animals or animals with basal forebrain cholinergic lesions do not improve the performance of senescent animals. While vigilance performance is impaired in senescent animals, the behavioral components of this impairment differ from animals with experimentally induced manipulations of the cholinergic system; thus, speculations about the neuronal substrate of the impairment in senescent animals are not available. Generally, normal aging in rats may not represent a useful experimental variable in experiments designed to explore the variables contributing or determining the putative beneficial effects of pharmacological treatments on cognitive processes mediated by cholinergic systems.

REFERENCES

Fischer, W.; Nilsson, O.G.; Bjorklund, A. In vivo acetylcholine release as measured by microdialysis is unaltered in the hippocampus of cognitively impaired aged rats with degenerative changes in the basal forebrain. Brain Res. 556:44–52; 1991.

ACKNOWLEDGMENTS

This research was supported by Public Health Service grants RO1 AG10173 and KO2 MH01072 to Dr. Sarter.

The authors thank Dr. D.N. Stephens (Schering AG, Berlin) for the gift of ZK 93,426 and Dr. Colin Gardner (Roussel, Swindon, U.K.) for the gift of RU 33965.

Address correspondence to Dr. Martin Sarter, Department of Psychology and Neuroscience Program, The Ohio State University, 27 Townshend Hall, Columbus, OH 43210.


Muir, J.L.; Everitt, B.J.; Robbins, T.W. Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. Psychopharmacology 118:82–92; 1995.


Received May 1, 1995

Accepted September 18, 1995