

The effect of R 58 735 (Sabeluzole) on memory functions in healthy elderly volunteers

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Abstract. The effects of chronic treatment (5 mg b.i.d. for 2 days followed by 10 mg b.i.d. for 5 days) with R 58 735 on human memory functions were studied in healthy elderly (age ≥ 50 years) volunteers in a double-blind placebo-controlled study. Serial learning of nonsense syllables was better under R 58 735, and relearning 1 week after termination of the treatment was superior to relearning of similar material initially learned under placebo. Free recall of nonsense syllables was significantly better when these were learned under active compound. Proactive inhibition induced by consecutive presentation of word lists was attenuated by R 58 735. Short-term memory functions, retrieval accuracy from semantic memory and unprepared reaction times were unchanged. R 58 735 ameliorated both learning and recall in conditions of age-related mild hypofunction in healthy volunteers. The compound seems to have had positive effects on encoding and consolidation of new material.

Key words: Memory – Serial learning – Proactive inhibition – Nonsense syllables – R 58 735 – Sabeluzole

R 58 735, a chemically new benzothiazol derivative (Fig. 1), has been shown to have a pharmacological profile consisting of three major activities in experimental animal models. First, it is an effective protector against several types of hypoxia (Wauquier et al. 1986). Second, it has an antiepileptic profile which resembles that of carbamazepine (Wauquier et al. 1986). Finally, the compound seems to have unique and specific effects on memory and learning in both rats and guinea-pigs (Clincke and Sahgal 1986; Wauquier et al. 1986). The 3-month toxicity studies in rats and dogs showed R 58 735 to be a safe drug (Verstraeten et al. 1986a, b).

In healthy volunteers this drug has a favourable phar-

macokinetic profile (Van de Velde et al. 1987). In general, it is well tolerated and does not adversely affect haemodynamic, biochemical or haematological parameters. The combination of safety and high bioavailability indicated that this drug might be potentially useful in chronic diseases.

Impaired memory function is not just an early indicator of developing dementia, but occurs in a mild form as a natural consequence of aging (Corkin et al. 1985). Given the favourable effects of the new drug on animal cognition and the increasing importance of disturbed cognition in our rapidly aging population, it was decided to study the effect of R 58 735 on memory functions of elderly healthy volunteers.

Materials and methods

Study design

The entire experiment lasted 4 weeks. During the 1st week, 12 volunteers were given either R 58 735 or placebo in a double-blind randomized order. This was followed by a placebo treatment for all the volunteers during the 2nd week. A cross-over was performed during the 3rd week. Those who received R 58 735 during the first treatment period were then given placebo and vice versa for the other group. During the 4th week no treatment was given. Test sessions were held at the end of each treatment week.

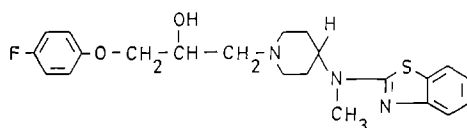
Subjects

Twelve healthy elderly volunteers (11 male, 1 female), with a median age of 59 years (extremes 50, 64), a median weight of 72 kg (extremes 56, 97) and a median height of 1.74 m (extremes 1.66, 1.83) were included in the study. All were professionally active individuals.

Instructions

One week before the onset of the experiment all volunteers were briefed individually. They were given a short demonstration of all the test that were scheduled to be used. This was done in a random order and with material that was different from that used in the actual experiment. They were informed that some tests could be given more than once (without specification) and that the order would vary. All volunteers were explicitly asked not to rehearse between sessions.

They were instructed to take their medication at exactly



R 58 735

Fig. 1. Structural formula of R 58 735

12-h intervals together with some food. The last tablet had to be taken at exactly 2.5 h before the onset of each test session. All volunteers gave their informed consent.

Medication

Both R 58 735 and placebo were given as divisible 10 mg tablets. For each treatment week the intake schedule was as follows: half a tablet b.i.d. for the first 2 days, followed by one tablet b.i.d. for the remainder. As the terminal plasma half-life is 22 h in normal healthy volunteers, a 1-week treatment period was chosen to obtain steady-state plasma levels at the time of testing.

Test battery

Word lists. This test consisted of the consecutive presentation of four equivalent word lists of ten Dutch words each. They were matched for word length and category specificity. Each list contained ten words belonging to ten different categories (Rosch 1975). The position of the words in the list was randomized but the presentation order was the same for all volunteers.

The words, written in capitals, were presented (2 s), one at a time on the monitor of a BBC personal computer unit, separated by asterisks (2-s intervals). Subjects were instructed to learn the first list and to read each word aloud as it appeared on the screen. Two seconds after the last word, instructions to count back aloud for 30 s were given on the screen. This arithmetic task was generated at random by the computer. A number between 13 and 25 had to be subtracted from a number between 4000 and 5000. Subsequently, the subjects were given 30 s to recall the words from the list. The whole procedure was repeated for lists 2, 3 and 4.

The number of correctly recalled words, as well as the number of interfering words from previous lists, was noted.

Recognition test. Two pages of 60 words each were given to the subjects. Ten per cent came from the original four lists described under "Word lists". More specifically, all words in positions 2, 5 and 8 of each list were selected. The other masking words belonged to the same ten categories mentioned above. The subjects were asked to encircle the words they recognized as coming from the original lists. The subjects were unaware of the number of words hidden.

The total number of marked words, as well as the number of correctly recognized words, was counted. The score was corrected for the 10% probability of indicating a right word by chance. The corrected score was thus defined as number correct — (total number marked $\times 0.1$). The time needed for completing the pages was measured.

Nonsense syllables. A classical Ebbinghaus serial learning task with 12 consonant-vowel-consonant trigrams was used.

The nonsense syllables, which appeared in capitals, were presented during 2 s one at a time on the monitor of a BBC personal computer unit, separated by asterisks (2-s intervals). Subjects were instructed to read each syllable aloud, character by character, as it appeared for the first time on the screen. The whole list was repeated ten times with the trigrams in the same order. From the second presentation on, they were asked to predict the trigram which was going to appear following the asterisk. The number of correct predictions per presentation was counted.

Digit span. Forward and reverse digit span was determined by reading rows of digits aloud at a rate of one digit per second.

For the supra span a row of figures containing two more digits than the actually determined forward digit span was read as often as necessary (maximally ten repetitions) until they could be repeated by the subject in the correct order.

Semantic memory retrieval. A type written list of 50 sentences bearing upon general knowledge was presented to the subjects.

To measure retrieval from semantic memory, the subjects had to evaluate the veracity of as many short sentences as possible for 1 min. The number of sentences read and the accuracy of the judgement were measured. Accuracy was defined as number correct over number read.

Paired associates. Ten pairs of words were shown consecutively on the screen. Words were presented one at a time (2 s) and pairs were separated by asterisks. For five pairs the association was obvious, for the others it was weaker. The whole series was repeated five times with varying presentation order. The words were read aloud during their first appearance. From the second time on, the subjects had to predict the second word of the pair upon presentation of the first. The number of correct predictions was counted.

Mirror learning. Four lists of eight words each with varying length (extremes 5, 18 letters) were presented one at a time for 2 s. All words appeared in mirror writing on the screen and had to be read aloud. The first two lists were in capital letters, the remaining two in small print. The number of correct readings was counted.

Unprepared reaction time. During 1 min, the numbers 1 and 2 appeared on the computer screen in a random order. The subjects had to respond by immediately hitting the corresponding keys on the keyboard. When the wrong key was touched, a bell sounded and the presentation of digits was stopped until the right key was hit. In a 1 min trial, the number of correct hits in every 10-s period was recorded.

Test sessions

Test session 1. At the end of the 1st treatment week, the following tests were presented to the subjects in the order listed below:

1. Word lists
2. Forward digit span
3. Supra span
4. Semantic memory retrieval
5. Nonsense syllables
6. Reverse digit span
7. Unprepared reaction time
8. Free recall after 30 min of word lists (see 1)
9. Free recall after 5 min of nonsense syllables (see 5)

Test session 2. At the end of the 2nd treatment week (all single blind placebo), the following tests were presented to the subjects in the order listed below: