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EFFECTS OF SOMATOSTATIN-14 ON ACTIVE AVOIDANCE BEHAVIOR IN FEMALE RATS.

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Somatostatin (SST), a tetradecapeptide, is considered to be one of the important neuromodulators in the central nervous system (Epelbaum, 1994). It is present in the central nervous system (Reubi, 1997), the hypothalamopituitary system, the gastrointestinal tract, the exocrine and endocrine pancreas, and the immune system (Reichlin, 1983). In the central nervous system, SST is mainly distributed in the cerebral cortex, hippocampus, and hypothalamus (Chan-Palay, 1987; Johansson et al., 1984). It is well known that the cerebral cortex and hippocampus are integrative regions of cognitive functions. Considerable effort has been made to investigate the behavioral, neuropharmacological, and neurochemical effects of somatostatins (Somatostatin-14 and Somatostatin-28). The first indications of behavioral effects of these peptides were demonstrated in monkeys (Siler et al., 1973). In rats, the peptides influence self-stimulatory behavior (Vécsei et al., 1982), active (Vécsei et al., 1987) and passive (Vécsei et al., 1990a; Romanova et al., 1990) avoidance behavior, and motor behavior (Vécsei et al., 1984) and display anti-amnestic action (Vécsei et al., 1983). A thiamine-difficient diet significantly impaired avoidance learning in proportion to decrease of SST fluorescence intensity in several brain regions (Nakagawasai et al., 2000a; Nakagawasai et al., 2003). It also has been demonstrated that brain somatostatin is one of the most severely affected systems in patients with Alzheimer's disease (Davies, 1980; Vécsei and Klivényi, 1995), suggesting its possible involvement in the memory deficit of these patients. FK 962 improved the memory impairments in rats through a possible potentiation of hippocampal somatostatinergic neurotransmission (Tokita et al., 2005). This study strengthens the view that FK962 might be of therapeutic value against dementing disorders such as Alzheimer's disease or senile dementia of the Alzheimer's type.

The aim of the present study was to examine the effects of two different doses (0.5 and 1 μg) of SRIH-14 on learning and acquisition of learning in adult female rats.

Adult female Wistar rats weighing 210-230 g at the time of operation were implanted with a headset (later serving for i.c.v. injections) under ether anaesthesia. A minimum recovery period of 5 days was permitted before the onset of experiments. The animals were divided into three experimental groups, each including 8 rats. The first (I) and second (II) groups consisted of rats given a single i.c.v. injection of 0.5 or 1.0 μg of SRIH-14 (S9129; Sigma, St. Louis, MO. USA) in 5 μL of saline, respectively, three times every 48 hours. Rats of the third (III) (control) group were treated in the same manner with an equal volume of saline alone. Learning in the rats was examined by testing of active avoidance of a painful stimulus in an automated "Shuttle box 450" cage. A tone of 1000 Hz and 68 dB for a maximum of 10 s was used as the conditioned stimulus (CS). The unconditioned stimulus (US) was an electric shock (0.2 mA, 2 s) delivered through the grid floor of the cage to the paws of the rat. The CS was presented for 8 s or terminated as soon as the animal made the response. The rats were tested on five consecutive days, 30 min after i.c.v. administration of 0.5 or 1.0 μg of SRIH-14 or saline on days 1, 3 and 5. Each day for five consecutive days, 10 trials were performed with inter-trial intervals of 60 seconds. For adaptation to the cage environment, the animals were put in the cage 15 minutes before the testing. The number of correct answers (CARs – conditioned avoidance responses) out of 10 trials per day was registered during the test performance. An answer was considered correct when the animal crossed the cage to the other side during the tone application to avoid the painful stimulus. The conditioned avoidance responses (CARs) from each rat were averaged per experimental group and standard deviation (SD) of the means was calculated. One-way analysis of variance (ANOVA) was used to test differences between the days of treatment within each experimental group. A statistically significant difference was considered to be one with a probability of 5% and less. The effects of SRIH-14 on shuttle-box learning in female rats are presented in Fig. 1.

In the control group, we obtained an increase of conditioned avoidance responses (CARs) from the first to the fifth experimental day, although these increases were not statistically significant ($p>0.05$). In group I (0.5 μg SRIH-14), there was a statistically significant increase of CARs ($p < 0.05$) on the fifth experimental day in comparison with the first and the second experimental day. In group II (1.0 μg SRIH-14), there was a statistically significant increase of CARs ($p < 0.05$) on the fifth experimental day only when compared to the first experimental day. As seen in Fig. 2, the total number of CARs for five consecutive days was increased in group II, but this increase was not statistically significant, probably due to considerable individual

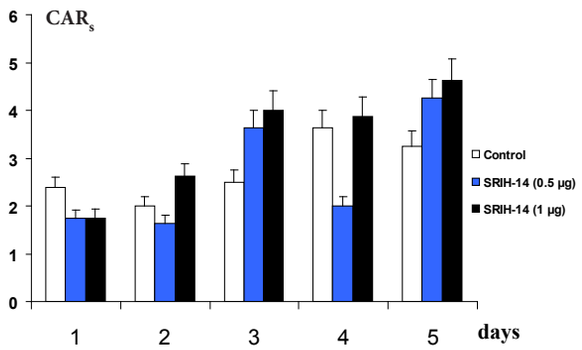

Fig. 1. Effects of SRIH-14 on shuttle-box learning in female rats. All values are means ± SD, n=8 animals per group. Arrows indicate the day of peptide injection. * p<0.05 versus the first and second day of 0.5 µg SRIH-14 treatment. † p<0.05 versus the first day of 1.0 µg SRIH-14 treatment.

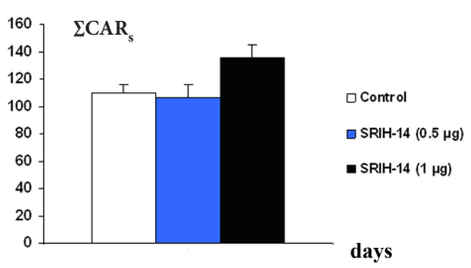

Fig. 2. Total number of CARS for five consecutive days in female rats; n=8 animals per group ± SD.

variability within each experimental group.

The present study evaluated the effect of SRIH-14 on active avoidance behavior in female rats. Also, the effects of two different doses of i.c.v. administered SRIH-14 were analyzed. Some previously reported data indicated that somatostatin-28, but not SRIH-14, influenced shuttle box learning in adult male rats (Vécsei et al., 1990a). Besides differences in the type of somatostatin used, sex differences should be also considered. All studies so far available were performed only in adult male rats (Vécsei and Widerlöv 1990b; Nakagawasai, 2000, 2003). Our previous studies (Starcevic et al., 2000) on adult female rats demonstrated that i.c.v. applied SRIH-14 and -28 exerted opposite effects on the immunohistochemical and morphometric characteristics of ACTH cells, as well as ACTH plasma levels. Since shuttle-box learning is a stressful learning paradigm, it is worth pointing out that i.c.v. applied SRIH-28, but not SRIH-14, exerted significant inhibitory effects on the function and morphometric characteristics of ACTH cells. Consequently, it is possible that SRIH-14, through its slight activation of the HPA axis, facilitates active avoidance learning in female rats.

In conclusion, our results obtained in female rats with both doses used support the hypothesis that SRIH-14 affects active avoidance behavior. Work involving specific pharmacological manipulation of central SRIH receptors must consider the SRIH type, doses, and sex differences in response to this peptide. Nevertheless, these findings could lead to modulation of learning processes without alteration of physiological activity evoked by SRIH.

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