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Teneurin C-terminal associated peptide (TCAP)-1 modulates dendritic morphology in hippocampal neurons and decreases anxiety-like behaviors in rats☆

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ABSTRACT

Teneurin C-terminal associated peptide (TCAP)-1 is a member of a novel family of neuropeptides that has been highly conserved throughout evolution. TCAP-1 is expressed in the limbic system in areas such as the hippocampus and amygdala. *In vitro*, TCAP-1 increases cytoskeletal proteins in immortalized neurons and modulates neurite outgrowth in cultured primary hippocampal neurons. *In vivo*, TCAP-1 blocks stress-induced c-Fos in the hippocampus and amygdala, and modulates stress-induced anxiety-like behaviors. This suggests that TCAP-1 plays a role in the remodeling of limbic system networks to alter stress behaviors. Dendritic spines on the apical and basilar shafts of hippocampal neurons are sensitive to stress and many receive incoming excitatory synaptic connections. In this study, repeated daily injection of TCAP-1 for 10 days increased spine density in the CA1 and CA3 regions of the hippocampus without affecting spine density in the amygdala. Further investigation of the CA3 region indicated that TCAP-1 did not affect the morphology of apical dendrites, but decreased branching in the basilar dendrites 90–130 μm away from the soma. Moreover, TCAP-1 treatment increased open arm time and decreased closed arm entries on the elevated plus maze, a test of anxiety-like behavior. These results suggest that TCAP-1 may be associated with anxiety-like behavior via regulation of dendritic morphology in the hippocampus, independent of amygdalar modification.

1. Introduction

The teneurin C-terminal associated peptides (TCAPs) are a novel family of neuropeptides found on the extracellular tip of the teneurin proteins [1]. One of these peptides, TCAP-1, is expressed throughout the brain and particularly in limbic regions including the hippocampus, amygdala, cerebellum, hypothalamus, and cortex [2]. TCAP-1 elicits both *in vitro* and *in vivo* effects. TCAP-1 is neuroprotective against alkalotic stress [3] and modulates cAMP accumulation [2]. Furthermore, a series of studies in rats indicate a role of TCAP-1 on the central corticotropin-releasing factor (CRF) system in the brain. TCAP-1 attenuates CRF-induced c-Fos immunoreactivity in the limbic system [4], notably in the hippocampus and amygdala. Further, TCAP-1 administration regulates a number of CRF-induced behaviors including acoustic startle [5], cocaine reinstatement [6], and elevated plus maze and open field performance [5,7]. Effects on behavior are long-lasting, with TCAP-1 effects persisting 21 days after peptide injection [2]. Although these studies indicate that TCAP-1 may have an effect on CRF regulation, and hence elements of the stress response, the mechanism by which this occurs is not known.

The hippocampus and amygdala are structures that are associated with the regulation of the behavioral stress response [8–10], and recent data indicate that these areas are important substrates for TCAP-1 action. Dendrites on the pyramidal neurons of these two regions are morphologically plastic, and dendritic branches can reversibly change in complexity in response to a variety of stimuli, such as stress [11,12] and learning [13]. The dendrites of these two areas also contain numerous spines, some of which receive excitatory synapses. The formation and pruning of spines is also highly neuroplastic. Stimuli such as chronic restraint or immobilization drastically alters the number of spines in the CA1 and CA3 regions of the hippocampus [14,15] and the basolateral nucleus of the amygdala [16,17], which involves the reorganization of cytoskeletal proteins and other elements [18,19]. *In vitro*, TCAP-1 increases cytoskeletal proteins in immortalized neurons, including β-actin and β-tubulin, and modulates neurite outgrowth in primary hippocampal cultures [20], which suggests that TCAP-1 has a role in regulating dendrite morphology and may modulate stress-related behaviors by inducing changes in the neural circuits in regulatory brain areas.

To test the hypothesis that TCAP-1 could affect morphology of such circuits, the role of TCAP-1 on the formation of dendritic spines in the

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hippocampus and amygdala was investigated. The CA3 region of the hippocampus was also further analyzed to test whether TCAP-1 affects dendritic branching. TCAP-1-treated animals were also tested to determine if TCAP-1 affects behavior in the elevated plus maze to establish whether the behavioral performance in this model could be related to morphological changes in dendrites.

2. Materials and methods

2.1. Animals

All experiments were performed using methods approved by the University of Toronto Animal Care Committee and the Canadian Council on Animal Care. Male Wistar rats (n = 15, 250–270 g, Charles River Laboratories, Montreal, QC) were individually housed in shoebox cages on a 12 h light/dark cycle (lights on a 0700 h) at a constant temperature of 21 °C, and were provided with standard rat chow and tap water *ad libitum*. The same group of animals was used for the behavior, spine density and dendritic arborization studies.

2.2. Surgery

Upon delivery, rats were allowed 1 week to acclimatize to housing conditions. Rats were anesthetized with 2–3% isoflurane and fit into a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). Before surgery, subcutaneous analgesics (0.5 mg buprenorphine) were administered. Rats were surgically implanted with a 22-gauge guide cannula (Plastics One, Roanoke, VA) into the right lateral ventricle (AP: -1.0, ML: -1.4 from bregma, DV: -3.7, from dura [21]). Guide cannulae were secured using four jeweler's screws and dental cement, and the opening was covered by a cannula dummy to ensure cannula patency. Rats were allowed to recover from anesthesia under warm heating lamps before being returned to their home cages and were allowed one week to recover from surgery.

2.3. TCAP and vehicle administration

Synthetic TCAP-1 was synthesized as described previously [2]. The lyophilized peptide was solubilized by exposure to ammonium hydroxide vapor for 2 min before dilution in phosphate-buffered saline (10 mM PBS, pH 7.4) at a concentration of 100 mM. Injections were delivered between 1000 h and 1200 h. Intracerebroventricular (i.c.v.) injections were delivered at a rate of 2 μl/min by a syringe pump (Razel Scientific Instrument Inc., Stamford, CT) connected by PE-50 tubing to a 28-gauge stainless steel injector needle that extended 1 mm below the cannula guide opening. Animals were injected once daily for 10 consecutive days with either 3 μl of 100 mM TCAP (300 pmol dose) or 3 μl of saline (control). The injector needle was left in place for 60 s following injection to prevent backflow up the cannula.

2.4. Elevated plus maze (EPM)

The animals were tested on the elevated plus maze (EPM) 24 h after completion of the 10-day injection regimen. The EPM test was conducted using a standard EPM apparatus, consisting of four arms (50 cm × 10 cm) with arms extending from a 10 cm × 10 cm central platform. Two arms were 180° apart and were enclosed by 40 cm opaque Plexiglas walls (closed arms) whereas the two other arms did not have walls (open arms). The EPM was elevated 65 cm from the floor by a post below the center platform. The entire maze was painted black. The rats were placed on the EPM facing one of the open arms and were allowed to freely explore for 5 min under low-light conditions. The EPM was cleaned with mild soap and ethanol between tests.

The animals were filmed from above, and their movements were quantified using the EthoVision tracking system (Noldus Information Technology, Utrecht, Netherlands). Only data from rats that completed the test were used. A minimum movement of 2 cm was required to be scored as genuine displacement. Other threat-assessment behaviors (head-dipping, stretched-attend, and rearing) were manually scored by observers blind to the study design.

2.5. Tissue fixation and histology

Twenty-four hours after the last injection treatment, rats were deeply anesthetized with 3% isoflurane and decapitated. The brain was removed within 2 min and dissected to obtain a tissue block between 1.0 mm and −7.0 mm from bregma [21]. Brain blocks were rinsed with PBS, placed in impregnation solution containing potassium dichromate, mercuric chloride, and potassium chromate (Solutions A and B, Rapid GolgiStain Kit, FD Neurotechnologies Inc, Ellicott City, MD), and were stored in the dark for 14 days. Brains were then rinsed and transferred to a cryoprotectant solution (Solution C) for 48 h, rapidly frozen in −70 °C isopentane and stored at −80 °C. Brain blocks were sectioned on a cryostat at −30 °C to obtain 100 μm slices through the dorsal hippocampus and amygdala. Brain sections were mounted on 3% gelatinized slides, air-dried in the dark, and stored in boxes at room temperature prior to staining. The brain sections were then rehydrated in ddH_2O and visualized in solutions D and E supplied by the manufacturer. The sections were then dehydrated in graded ethanols, cleared in xylene, and cover-slipped with Permount (Fisher Scientific). Slides were subsequently stored in the dark until analysis. All brains were checked for proper cannula placement under the microscope, and those with improper placement were removed from the sample population.

2.6. Dendritic spine analysis

Pyramidal cells from the CA1 and CA3 regions (−2.30 to −4.80 mm from bregma) of the hippocampus and from the BLA (−1.80 to −3.14 mm from bregma) were selected for quantitative analysis. For each brain, 5 CA1, 5 CA3, and 5 BLA neurons were analyzed. To be included in the analysis, Golgi-impregnated pyramidal cells had to be uniformly stained throughout the basilar and apical trees and discernible from neighboring cells. For the CA1 and CA3 regions, primary and secondary dendritic branches in the stratum oriens (starting from 25 μm away from the soma), and secondary and tertiary dendritic branches in the stratum radiatum (100–200 μm from the soma) and stratum lacunosum-moleculare (the most distal dendrites from the soma in the apical tree) were investigated. In the BLA, starting 25 μm away from the soma, primary and secondary branches were investigated. On each neuron investigated in each stratum, 5 segments of 10 μm each were photographed using an inverted microscope at 1000x with oil immersion (Leica 165 C Stereoscope, Richmond Hill, ON). In some cases, the segments were from the same branch. Dendritic spines from photomicrographs were manually counted using NIS Elements Software Basic v2.30 (Nikon, Mississauga, ON) by an observer blind to the study. Spines were required to be distinct from the dendritic branch to be counted. All protrusions, regardless of their spine type, were counted. Spine counts are underestimates because the above methods do not take into account spines that are obscured by the dendritic segment. We also did not analyze for possible changes in the dendritic diameter, which could alter the ability to count the spines.

2.7. CA3 dendritic branching analysis

Long and single-shafted pyramidal cells from the CA3 region from the dorsal hippocampus (−2.30 to −4.80 mm from bregma) were traced at 40x magnification using Neurolucida software (MicroBrightFields,

Williston, VT) with a Leica DMRB microscope fitted with a motorized XYZ stage. Analysis of neuronal tracings was performed with NeuroExplorer (MicroBrightFields). Sholl analysis [22] was performed on the number of intersections in consecutive concentric spheres from the soma. Total dendritic length and branching points (nodes) irrespective of distance from soma were also counted. For example, a branch order of one indicates dendrite branches emanating directly from the soma whereas a branch order of two indicates those branches resulting from a node of a first order branch. The investigator was blind to the identification of the experimental groups when performing the analyses.

2.8. Statistical analysis

For the spine density analysis, counts from each neuron were averaged for a cell mean, and five neurons from each animal were averaged for an animal mean for each stratum analyzed. The CA1 and CA3 regions were analyzed by two-way ANOVA, with "TCAP-1" and "stratum" as independent factors. For the BLA, individual student's t-tests were performed. For the dendritic branching analysis, morphological data was analyzed by two-way ANOVA, with "TCAP-1" and "radius" as factors. Behavioral data was initially analyzed by student's t-tests. Data was analyzed using GraphPad Prism v4.0. $P<0.05$ was considered significant. To further assess the effects of TCAP-1 on the behavioral phenotypes and to improve the effective power of this small-n experiment, we employed a linear-modeling analysis. Raw data was loaded into the R statistical environment (v2.5.1) and general linear models were fit to each behavioural measure. Each model was of the form: Phenotype Score = Baseline Level + TCAP-1 Effect. For each term in this equation, we extracted the estimates of magnitude (the coefficients of the linear model), the error estimates (the standard errors of the coefficients), and the probabilities that the coefficients are significantly different from zero were determined directly from t-distribution.

3. Results

In each of the treatment groups, Golgi-stained neurons in the CA1 and CA3 regions of the hippocampus and pyramidal-like cells of the BLA were easily identifiable. Representative dendritic segments are illustrated in Figs. 1A and 2A (hippocampus) and Fig. 3A (BLA). A representative photomicrograph and tracing of a CA3 hippocampal neuron is illustrated in Fig. 4A and B.

3.1. Dendritic spine analysis

Animal means were analyzed by two-way ANOVA with "TCAP-1" and "stratum" as independent factors. In the CA1 region of the hippocampus (Fig. 1B), TCAP-1 treatment had a significant main effect on spine density ($F_{1,24}=8.16$, $p=0.009$). TCAP-1 treatment increased spine density in the strata lacunosum-moleculare, radiatum and oriens by 19.5%, 8.0%, and 18.3% respectively over saline-treated controls. There was also a significant main effect of stratum ($F_{2,\ 24}=6.15$, $p=0.007$), indicating that there is a difference in spine density across the different strata. No interaction was detected between spine density and stratum ($F_{2,24}=0.471$, $p=0.63$). Bonferonni's *post-hoc* tests indicate that the stratum radiatum possessed a significantly greater density of spines than the strata lacunosum-moleculare or oriens ($p<0.05$).

In the CA3 region of the hippocampus, (Fig. 2B), TCAP-1 treatment had a significant main effect on spine density ($F_{1,\ 24}=18.2$, $p=0.0003$), increasing spine density in the strata lacunosum-moleculare, radiatum, and oriens by 43.4%, 55.9%, and 60.4% respectively compared to saline-treated controls. However, the stratum did not have any significant main effects ($F_{2,24}=0.0726$, $p=0.930$), nor were any interactions detected between TCAP-1 and stratum ($F_{2,24}=0.0848$, $p=0.919$).

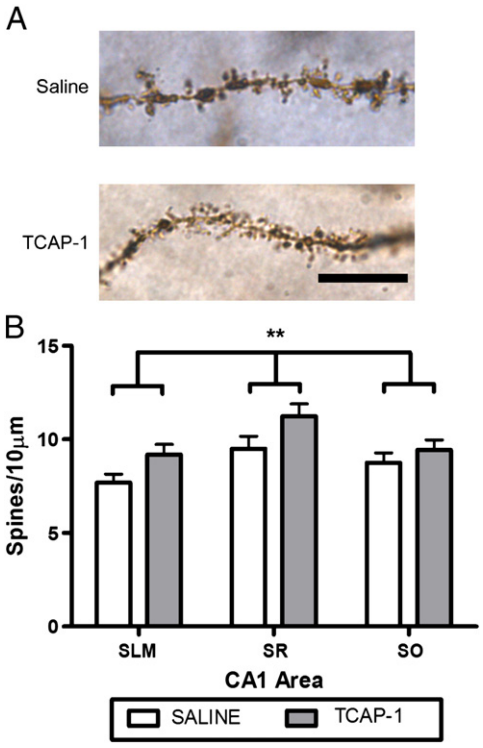

Fig. 1. Effects of repeated injections of TCAP-1 on dendritic spine density in the CA1 region of the hippocampus. (A) Representative photomicrographs of Golgi-stained dendrites of CA1 pyramidal neurons from the stratum radiatum treated with either saline (control) or TCAP-1 (i.c.v.) for 10 days. (B) Spine density counts from secondary and tertiary branches of the stratum lacunosum-moleculare (SLM) and stratum radiatum (SR) of the apical tree, and primary and secondary branches of the stratum oriens (SO) in the basilar tree. TCAP-1 had a significant main effect on spine density ($F_{1,24}=8.16$, $p=0.0087$, two-way ANOVA), increasing the number of spines in all three strata measured. Bars represent means ± SEM with $n=5$ rats per group (5×10 μm segments measured in 5 neurons per animal). Scale bar = 10 μm. $^{**}p<0.01$.

We did not detect any TCAP-1 induced alterations in spine density in the BLA region (Fig. 3B; $p=0.292$, *t*-test).

3.2. CA3 dendritic branching analysis

The CA3 region had the strongest response to TCAP-1 administration, and this area was further analyzed to determine the effects of TCAP-1 on dendritic branching in both apical and basilar shafts. A Sholl analysis was used to determine the effects of TCAP-1 on arborization as defined by the number of intersections made by dendrites in concentric spheres around the soma.

TCAP-1 administration had no effect the dendritic intersections on apical trees (Fig. 4C; $F_{1,450}=0.097$, $p=0.756$). However, TCAP-1 significantly decreased the number of dendritic intersections in the basilar tree (Fig. 4F; $F_{1,225}=13.9$, $p=0.0002$), specifically in the region 90–130 μm away from the soma, where dendritic branching was decreased by 21.6% ($p=0.035$, two-tailed *t*-test, Fig. 4F, inset). Irrespective of distance from the soma, TCAP-1 had no effect on total dendritic length in the apical (Fig. 4D; $p=0.72$) or basilar tree (Fig. 4G; $p=0.231$), and had no effect on the total number of branch points in the apical (Fig. 4E; $p=0.495$) or basilar (Fig. 4H; $p=0.280$) trees.

3.3. Elevated plus maze

Anxiety-like behavior on the EPM was measured by EthoVision software. Repeated injections of TCAP-1 resulted in greater open arm time (Fig. 5A; $p=0.0455$) and fewer closed arm entries (Fig. 5C; $p=0.008$), but had no effect on open arm entries (Fig. 5B; $p=0.962$)

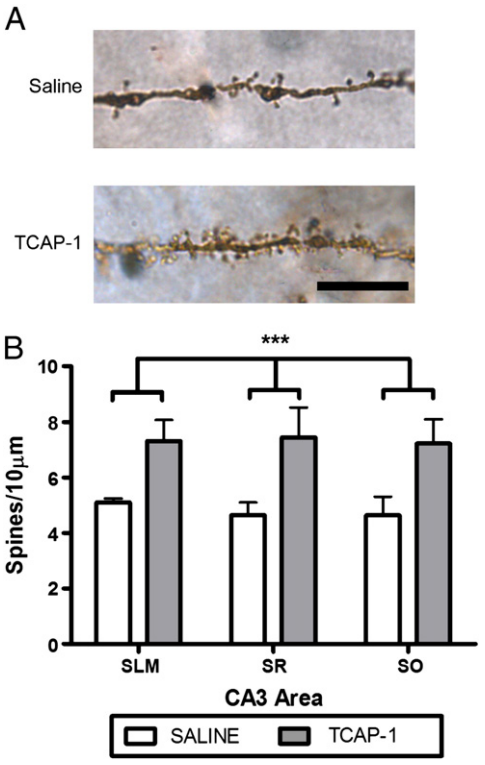

Fig. 2. Effects of repeated injections of TCAP-1 on dendritic spine density in the CA3 region of the hippocampus. (A) Representative photomicrographs of Golgi-stained dendrites of CA3 pyramidal neurons from the stratum radiatum treated with either saline (control) or TCAP-1 (i.c.v.) for 10 days. (B) Spine density counts from secondary and tertiary branches of the stratum lacunosum-moleculare (SLM) and stratum radiatum (SR) of the apical tree, and primary and secondary branches of the stratum oriens (SO) in the basilar tree. TCAP-1 had a significant main effect on spine density ($F_{1,24} = 18.3$, $p = 0.0003$, two-way ANOVA), increasing the number of spines in all three strata measured. Bars represent means ± SEM with n = 5 rats per group (5 × 10 μm segments measured in 5 neurons per animal). Scale bar = 10 μm. ***$p < 0.001$.

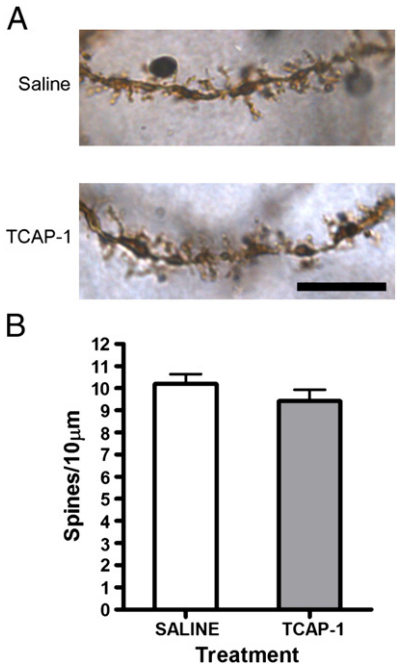

Fig. 3. Effects of repeated injections of TCAP-1 on dendritic spine density in the basolateral nucleus of the amygdala (BLA). (A) Representative photomicrographs of Golgi-stained dendrites of BLA pyramidal-like neurons treated with either saline (control) or TCAP-1 (i.c.v.) for 10 days. (B) Spine density counts from primary and secondary branches of dendrites. TCAP-1 had no significant effects on spine density in the BLA. Bars represent means ± SEM with n = 5 rats per group (5 × 10 μm segments measured in 5 neurons per animal). Scale bar = 10 μm.

relative to saline-treated controls. The significance of open-arm time and closed arm entries were $p = 0.0300$ and 0.0099, respectively, utilizing the linear modeling analysis. The assumptions of this approach differ from those of the ANOVA analyses, so the concordance of the two methods provides evidence that the results are robust to violations in modeling assumptions. TCAP-1 had no effect on threat-assessment behaviors (rearing, head-dipping, or stretched-attend; data not shown). There were no gross motor effects due to TCAP-1 as indicated by total locomotion on the EPM (data not shown).

4. Discussion

TCAP-1 is a novel peptide that is strongly expressed in the hippocampus, amygdala, cortex, and hypothalamus [2]. The present studies showed that TCAP-1, when injected i.c.v. over a period of 10 days, increased spine density in CA1 and CA3 hippocampal neurons but did not affect BLA neurons. TCAP-1 also decreased branching in the basilar tree of CA3 neurons. Furthermore, 10 days of TCAP-1 treatment significantly reduced anxiety-like behavior in the EPM test using the same group of rats utilized in the morphological studies, confirming that TCAP-1 changes in behavior can be seen under basal conditions.

Inputs to the CA1 and CA3 regions are laminar and come from sources unique to each stratum [23,24]. Cortical input arrives via the entorhinal cortex, which sends projections to the dentate gyrus via the perforant path and to the stratum lacunosum-moleculare in the apical shaft of CA1 and CA3 pyramidal neurons. Dentate gyrus mossy fiber input extends to thorny excrescences of the stratum lucidum of CA3 neurons. CA3 axons project to the CA1 via Schaffer collaterals to the strata radiatum and oriens of CA1 neurons. The CA1 then projects to the subiculum, the main output of the hippocampus. Intrinsically, axons of the CA3 project their axons both contralaterally and ipsilaterally to other CA3 neurons in addition to CA1 neurons and interneurons within the region [23]. These intrinsic projections terminate in the strata radiatum and oriens of CA3 neurons.

Ten days of TCAP-1 treatment increased spine density in the CA1 and CA3 regions across the different strata of the apical and basilar trees. There was no effect of strata in the CA3 region, as spine density between the three strata measured did not differ from each other. However, there was a significant effect of area in the CA1 region, as the stratum radiatum had more spines than the strata lacunosum-moleculare or oriens. This indicates that whereas TCAP-1 affects spine density in both the CA1 and CA3, it does not differentially affect strata of the dendritic trees. TCAP-1 did not affect BLA neurons, although TCAP-1 mRNA is expressed in the area and injections to the BLA produce modulatory effects in the acoustic startle test [2].

Increases in spine density in the strata radiatum and oriens of the CA3 suggest that TCAP-1 may have a role in intrinsic communication within the hippocampus. The CA3 region strongly expresses TCAP-1 mRNA [2] and peptide (Chand et al., manuscript in preparation), more so than the CA1. Therefore, the CA3 was also analyzed for changes in dendritic branching. Surprisingly, TCAP-1 decreased dendritic branching in the basilar tree (corresponding to the stratum oriens) but not the apical tree, although there was no change in the total length or branch points in either tree.

The increase in CA3 spine density in the stratum oriens but decrease in basilar branching indicates that overall spine availability may remain relatively unchanged in the basilar tree, as spine density changes as a function of dendritic length [25]. However, in the apical tree, there was no change in the branching but an increase in spine density, suggesting an increase in available spines. Together, this indicates that there is an increase in the apical, but not necessarily

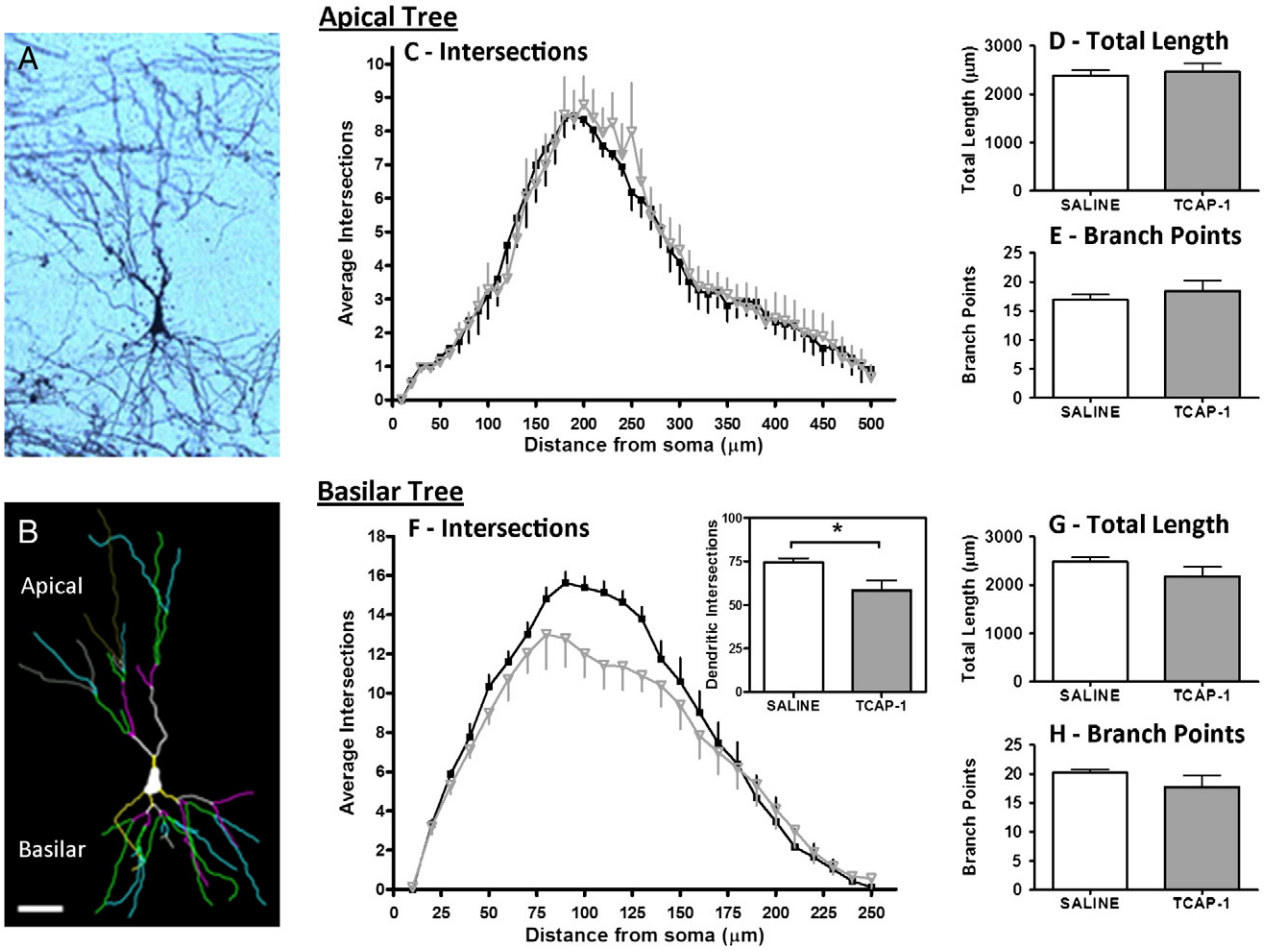

Fig. 4. Dendritic branching morphology in CA3 neurons of the hippocampus. (A) Brightfield photomicrograph of a Golgi-stained CA3 neuron with its (B) reconstruction in Neurolucida software showing both apical and basilar shafts. Different colors indicate branch orders. In the apical tree, ten days of TCAP-1 did not have any effects on (C) dendritic intersections using Sholl analysis, (D) total dendritic length, or (E) total branch points. In the basilar tree, TCAP-1 had a significant main effect on dendritic branching ($F; F_{1,225} = 13.9$, $p = 0.0002$), decreasing intersections in area 90–130 μm away from the soma (inset, $^*p < 0.05$, *t*-test). However, TCAP-1 did not have any significant effects on (G) total dendritic length or (H) total branch points in the basilar tree. Intersection points represent mean intersections + or - SEM whereas bars represent mean + SEM in saline (control, n = 5) and TCAP-1 treated (n = 6) rats. Scale bar = 50 μm.

basal, dendritic spine availability of CA3 neurons, although one should note that an increase of spines does not necessarily equate with an increase in synapses, as a proportion of synapses are "silent" and lack AMPA receptors [26]. Further studies that investigate the role of TCAP-1 on the type of spines and their receptor disposition will be required to determine if TCAP-1 has a role in increasing excitatory synapse input into the CA3 region.

These studies provide new insight into the role of TCAP-1 in the hippocampus and support previous studies indicating a significant role in this region of the brain. TCAP-1 increases β-actin and β-tubulin in immortalized neuron culture and increases neurite outgrowth in primary hippocampal neurons [20]. Dendritic remodeling depends on reorganization of the actin cytoskeleton, which mediates the formation, elimination, and stability of spines, and the microtubule

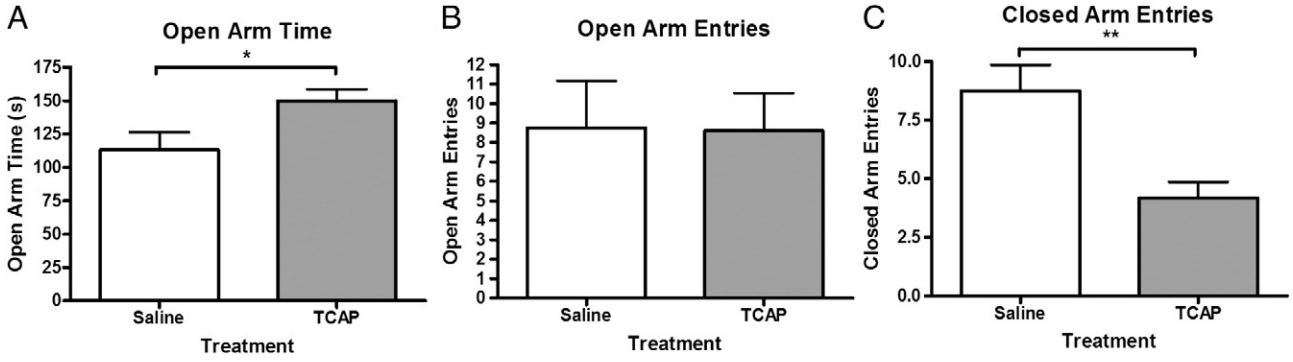

Fig. 5. Behavior on the elevated plus maze (EPM) to investigate the effects of 10 days of i.c.v. TCAP-1 treatment. TCAP-1 significantly increased open arm time (A) and decreased closed arm entries (C), but did not affect open arm entries (B). Data are means ± SEM in saline (n = 4) and TCAP-1 treated (n = 5) animals that completed the test and were analyzed for spine density changes. $^*p < 0.05$, $^{**}p < 0.01$.

cytoskeleton, where new spines anchor their actin filaments [27]. However, it remains to be seen whether TCAP-1 can affect other components of the actin cytoskeleton, such as microtubule-associated protein-2 (MAP2) and synaptopodin, which have been implicated in anxiety disorders in human patients [28] and microtubule-associated protein-1 (MAP1) and synaptophysin, which are increased and decreased respectively in the hippocampus after restraint stress [29].

The observed changes in spine density formation provide a mechanism that explains, in part, changes in the tested behaviors. Ten days of injections of TCAP-1 significantly increased open arm time and decreased closed arm entries on the EPM. In the EPM, rats will naturally avoid the open arms of the maze as the open space invokes a stress response [30]. Anxiolytic treatments, such as benzodiazepines, will increase open arm time and entries in the EPM [31,32]. In previous experiments, TCAP-1 had no effect under unstressed conditions [4,5,7] whereas effects in the absence of a stressor were seen in this study. As the previous studies utilized injections of 1 or 5 days, this suggests that longer treatment regimens may be required to see effects under unstressed conditions.

Few studies have compared spine density and anxiety-like behavior in the same animals. A recent study in female rats reported a negative correlation between escape tendencies in a learned helplessness paradigm and hippocampal synapses [33], indicating that an increase in hippocampal spine synapses is correlated with a decrease in depressive-like behavior. A study in humans correlated fewer spines in the CA3 with increased trait anxiety [28]. The data in this study suggest that an increase in spines may be associated with decreased anxiety-like behaviors, however, more studies will be required to elucidate the behavioral effects of animals under longer regimens of TCAP-1 treatment. Our study, therefore, appears to be the first to examine anxiety-like behavior, spine density and dendritic arborization in the same group of animals.

In summary, the present studies indicate that i.c.v. TCAP-1 can increase spine density in the CA1 and CA3 neurons, but not BLA neurons. TCAP-1 also decreases dendritic branching in the basilar tree of the CA3. Furthermore, TCAP-1 reduced anxiety-like behavior in one test of anxiety. Taken together these data suggest that TCAP-1 may be an important modulator of dendritic remodeling in the limbic region and particularly within the hippocampus.

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