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A specialized nutritional formulation protects against memory deficits induced by intracerebroventricular infusion of amyloid-ß peptide oligomers (AßOs) in mice.

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• Purpose:

Along with brain oxidative stress, lipid peroxidation and neuroinflammation, brain glucose hypometabolism and accumulation of the amyloid-ß peptide (Aß) are hallmark features of Alzheimer's disease (AD) and induce synapse failure and cognitive impairment.

We thus hypothesized that a specialized nutritional formulation providing ketone bodies as an alternative source of brain energy as well as antioxidant and anti-inflammatory nutrients could be protective in AD. Intracerebroventricular (i.c.v.) infusion of amyloid-ß oligomers (AßOs) in mice constitutes a validated method that induces memory deficits, glucose intolerance and neuropathological changes characteristic of AD.

The goal of the current study was to determine whether supplementation with a specialized nutritional formulation (henceforth demoted AZ formulation) might prevent memory loss induced by AßOs in mice.

• Methods:

Male Swiss mice aged 3 months were used. Animals were pre-treated with AZ formulation or an isocaloric placebo formulation for 4 weeks orally by gavage. Four experimental groups with 12 animals each were used: 2 groups received the placebo formulation and 2 groups received the AZ formulation. After treatment for 4 weeks, animals were infused with 10 picomol AßOs (or equivalent volume of vehicle solution) via i.c.v. in a final volume of 3 microliters.

For memory evaluation, animals were assessed in the Novel Object Recognition (NOR) test at 24 hours and 7 days after infusion of AßOs. The exploration times of both novel and familiar objects were measured.

The increase in exploration of the novel object (N) in relation to the familiar object (F) indicates that the animal was able to form a recognition memory.

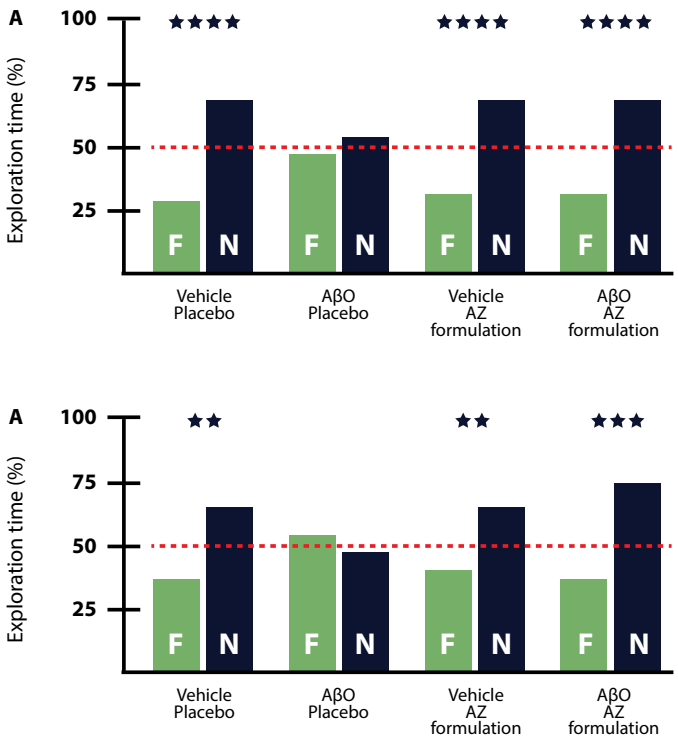
• Results:

In the NOR training sessions, animals explored similarly (~ 50% of the time) two equal objects(A1 and A2), indicating absence of innate preferences for object or location in the test arena. Consistent with our previous reports, the NOR test performed 24 hours after i.c.v. infusion of AßOs (Fig. 1A) showed that animals that received infusion of AßOs presented memory deficit. Interestingly, treatment with the AZ diet prevented memory loss caused by infusion of AßOs. Similarly, treatment with the AZ diet prevented memory deficit 7 days after infusion of AßOs (Fig. 1B).

• Conclusion:

Prior administration of the AZ formulation was effective in preventing short-term memory deficit caused by i.c.v. infusion of AßOs in mice, both 24 hours and 7 days after infusion of AßOs. Under identical experimental conditions, the control diet (placebo) had no protective effect.

Figure 1. NOR memory assessment 24 hours (A) and 7 days (B) after i.c.v. infusion of A.Os.



*Familiar and novel objects are indicated by F and N, respectively. Experimental groups: Placebo diet/vehicle: N = 11; A.Os/placebo diet: N = 11; Vehicle/AZ diet: N = 12; A.Os/AZ diet: N = 11. Bars correspond to means +- SEM; symbols correspond to individual animals. ****p<0.0001, ***p<0.001 **p<0.01 (statistically significant difference; one-sample t-test, comparing the percentage of exploration of the novel object to 50% ("chance level", represented by red dashed lines).*

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Effect os a specialized nutrition formulation in an animal model of alzheimer's disease.

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• Rationale:

Nutritional factors influence the risk of developing Alzheimer's disease (AD) and its rate of clinical progression. In rodents, models mimicking AD, can be used to study whether nutrition can improve cognitive alterations. One of these models, the applying of intracerebroventricular (ICV) streptozotocin (STZ), culminate in a neuroinflammatory picture with cognitive alteration.

• Methods:

Rats were randomly divided into two groups: sham and STZ. STZ group received a single bilateral ICV injection of STZ (1 mg/kg total dose) dissolved in sterile 0.9% saline. Sham group received a single bilateral ICV injection of 0.9% saline. Treatment with an antioxidant and anti-inflammatory nutritional formulation (AZ) (1 g/kg, per os) or its vehicle (0.9% saline) was performed over 30 days, once a day (n = 6– 10 per group). The animals were assessed in the open field test (OFT) to evaluate locomotor activity (day 27). Cognitive performance was evaluated (day 28), in the object recognition test (ORT) and in the spatial version of the Y maze. On day 30, they were deeply anesthetized and intracardially perfused for the immunohistochemical of doublecortin (DCX; marker of newborn and migrating neurons) and Iba-1 (microglial activation marker). Group differences were analyzed using one way analysis of variance (ANOVA) with Bonferroni's post-hoc test, with $p < 0.05$ (significant).

• Results:

Locomotor activity in the OFT did not reveal any changes in the locomotion parameters in all of the groups. STZ-lesioned rats showed a reduction in memory process in both ORT and Y maze. Besides, an increase in IBA-1 in the CA1 and CA3 (region of hippocampus). Most importantly, the treatment with AZ formulation was able to reverse the memory impairment observed in the ORT and Y maze and also reduced IBA-1 in the CA-1 and gyrus dentatus region of hippocampus.

• Object Recognition Test

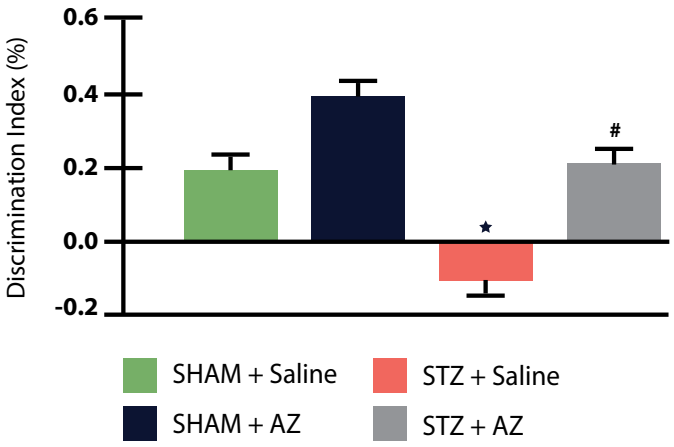

*FIGURE 1. COGNITIVE PERFORMANCE EVALUATION OF AZ FORMULATION EFFECTS IN STZ INJECTED ANIMALS COMPARED WITH SHAM ANIMALS The data are expressed as mean (±SEM. N=6-10 per group. *p<0,05,**p<0,01 vs. sham group; #<0,05, vs. STZ group (one-way ANOVA with Post Hoc de Bonferroni).*

• IBA 1 Immunorreacitivity / GD

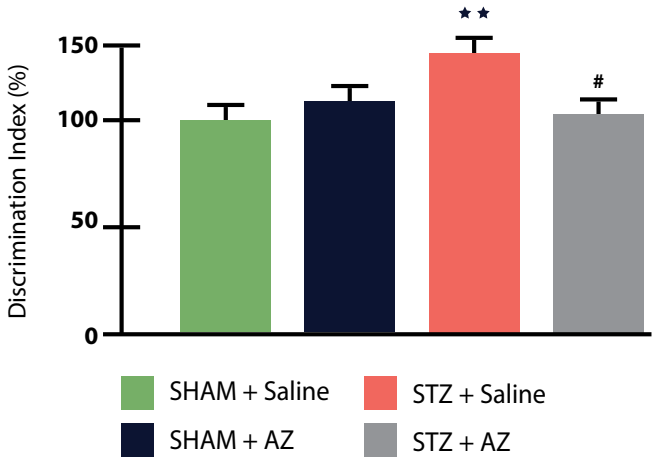

*FIGURE 2. AZ FORMULATION EFFECTS ON MICROGLIAL CELLS (IBA 1 IMMUNORREACTIVITY) IN STZ ICV ANIMALS The Iba 1 IR significantly increased in the GD area of hippocampus in STZ ICV rats, 30 days after surgery. The formulation AZ decrease Iba 1 IR significantly in the GD area of hippocampus. The data are expressed as mean ±SEM. n=4-6 per group. **p<0,01 vs. sham group; #<0,05, vs. STZ + saline group (one-way ANOVA with Post Hoc de Bonferroni).*

• Conclusions:

STZ-lesioned rats present a memory impairment besides the increase in microglial activation. The prolonged treatment with AZ formulation was able to counteract these changes.

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