

# Behavioral and neurochemical alterations induced by chronic treatment with AS101 in a rat model of depression.

Saida H.<sup>1,2</sup>, Gersner R.<sup>2</sup>, Zangen A.<sup>2</sup> and Sredni B.<sup>1</sup>

<sup>1</sup>The Safdie Institute for Cancer, Faculty of Life Science, Bar-Ilan University, Ramat-Gan, Israel. <sup>2</sup>Weizmann Institute of Science, Neurobiology Department, Rehovot, Israel.

### Purpose:

Depression is the second leading cause of disability worldwide, with only 50% of all patients showing full remission. Recent finding points to dramatic involvement of both brain-derived neurotrophic factor (BDNF) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPA) in depression. Antidepressant treatment is accompanied with increase levels of those proteins, mainly in the hippocampus. Amonium-trichloro-(dioxoethylene-O,O''-)-tellurate (also named AS101) is a non-toxic compound with pleiotropic activities, that was previously found to increase BDNF levels in vitro. Here, we examined AS101 potential as an anti-depressant.

### Methods:

AS101 was tested in 2 models of depression: the chronic mild stress (CMS), and a novel genetic model that was developed in our lab (depressed rat line; DRL).

In both models, different doses of AS101 were administrated i.p. for 14 consecutive days and the behavioral outcome was measured. Behavioral tests included sucrose preference, novel environment exploration, home-cage locomotion, forced swim-test and Morris water maze. Following those tests, the levels of BDNF and the AMPAR subunit GluR1, at reward-related brain areas, were analyzed by ELISA and Western blot.

### Procedure:



**Experimental design:** (A) 8 weeks old rats were exposed repeatedly to several unpredictable stresses (disruption of light dark cycle, food/water deprivation, tilt of the cages, strobe light during the night, white noise for a few hours and group housing ) after which they received AS101 daily i.p injections and behavioral tests were conducted. (B) 8 weeks old DRL received AS101 i.p injections for 14 continues days and behavioral tests were conducted.

### Results:

Both rat models (e.g rats after CMS exposure or animals from the DRL) demonstrated depressive-like behavior, while administration of AS101 had positive effect in both models.

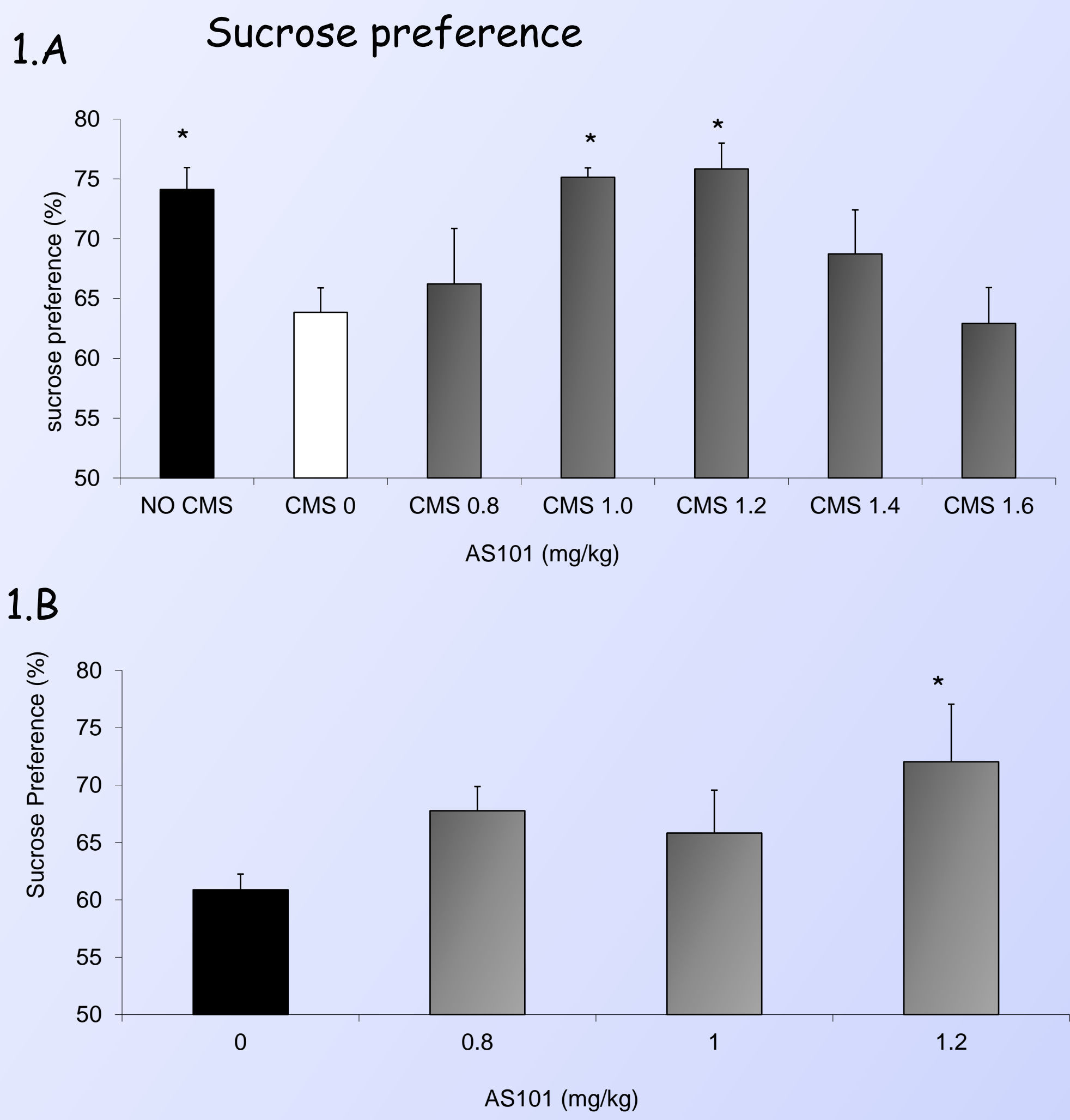


Fig 1. Specific doses of AS101 normalize depressive-like behavior either in the CMS model (A) or the DRL model as measured by Sucrose preference test. Sucrose percentage (0.2%) intake as calculated from total liquid consumption and compared to the CMS 0 group (A) or to Control group (B). \* p < 0.05

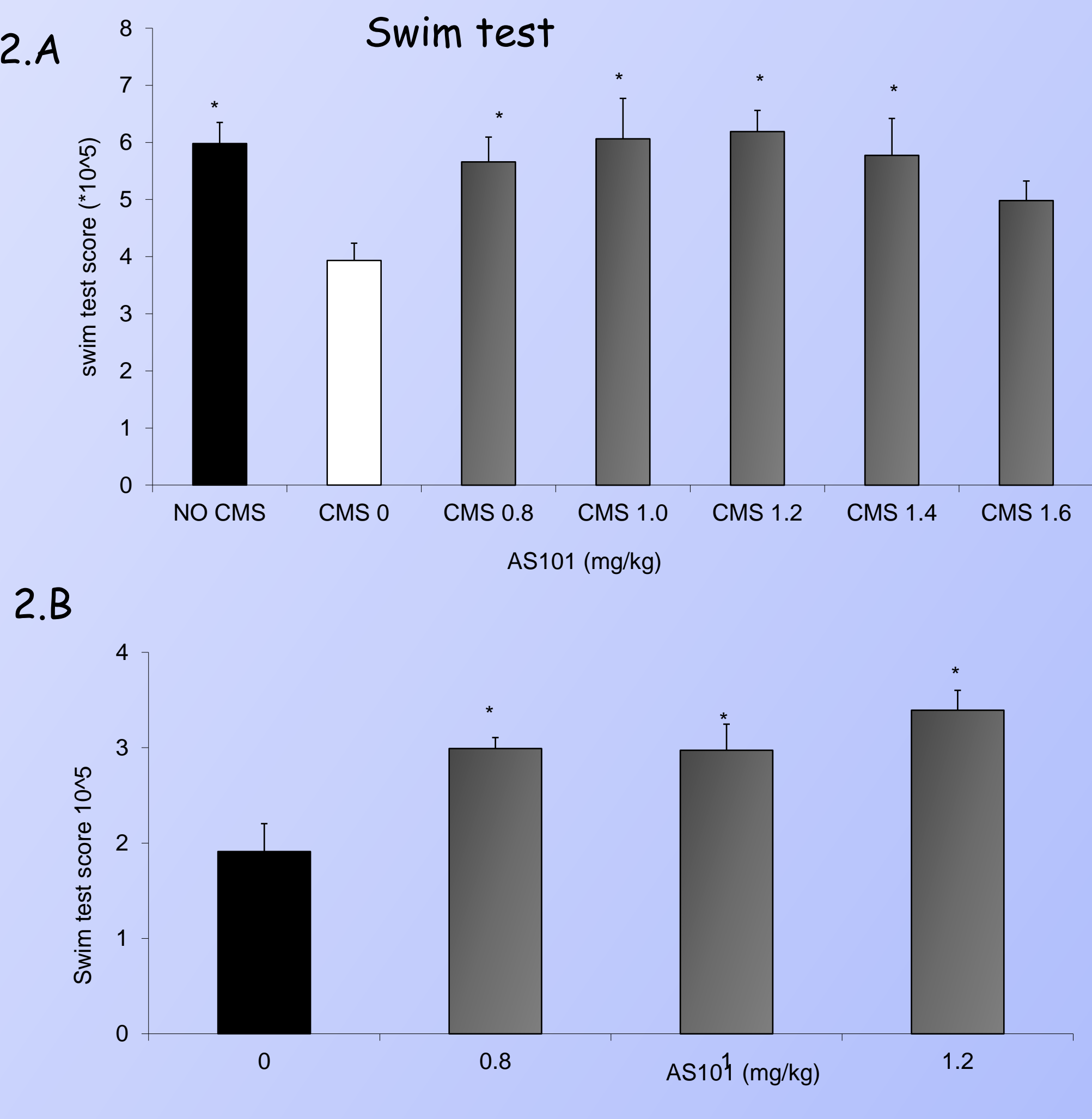


Fig 2. AS101 treatment effect rats activity in a modified forced swim test (FST) either in the CMS model (A) or the DRL model (B). The effect of AS101 on the mobility in the modified FST were videotaped, and activity was scored and analyzed using our locally developed software. \* p < 0.05 for AS101 treatment VS CMS 0 group (A) or AS101 treatment VS control group (B)

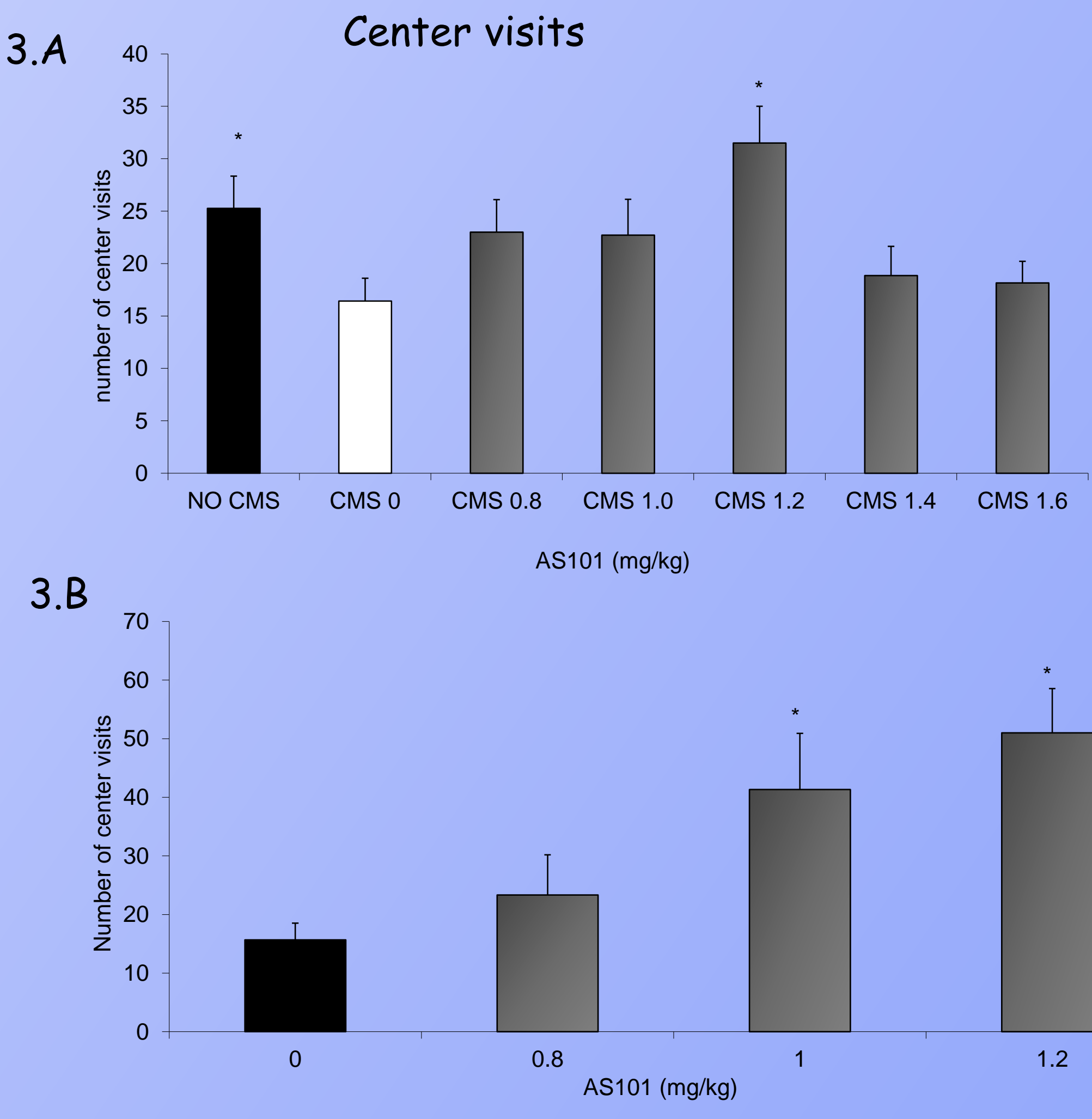


Fig 3. Specific doses of AS101 increased the number of center visits in the Exploration of a novel environment paradigm either in the CMS model or the DRL model. No effect was found on rearing and total distance. \*P<0.05 for AS101 treatment VS CMS 0 group (A) or AS101 treatment VS control group (B)

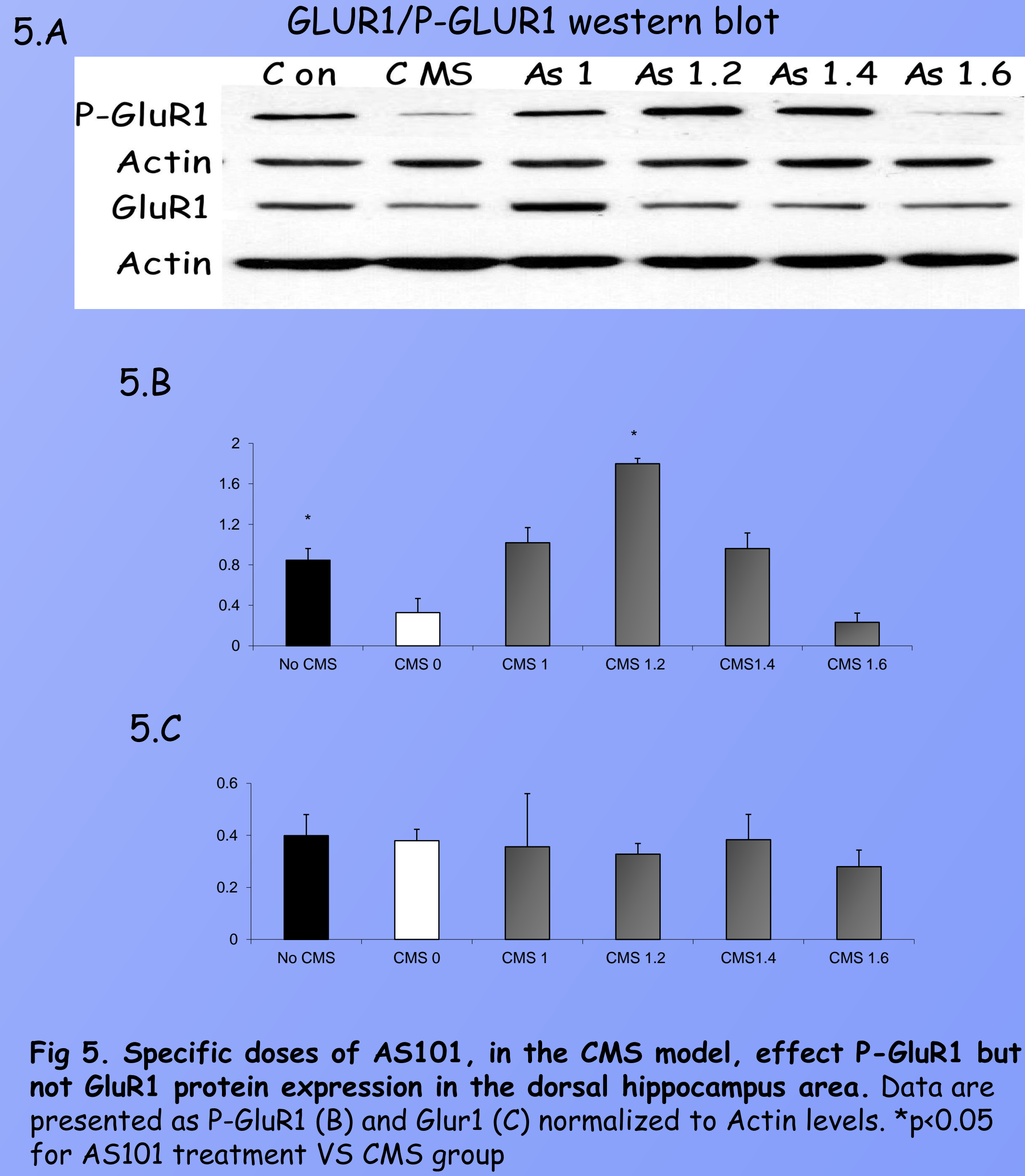
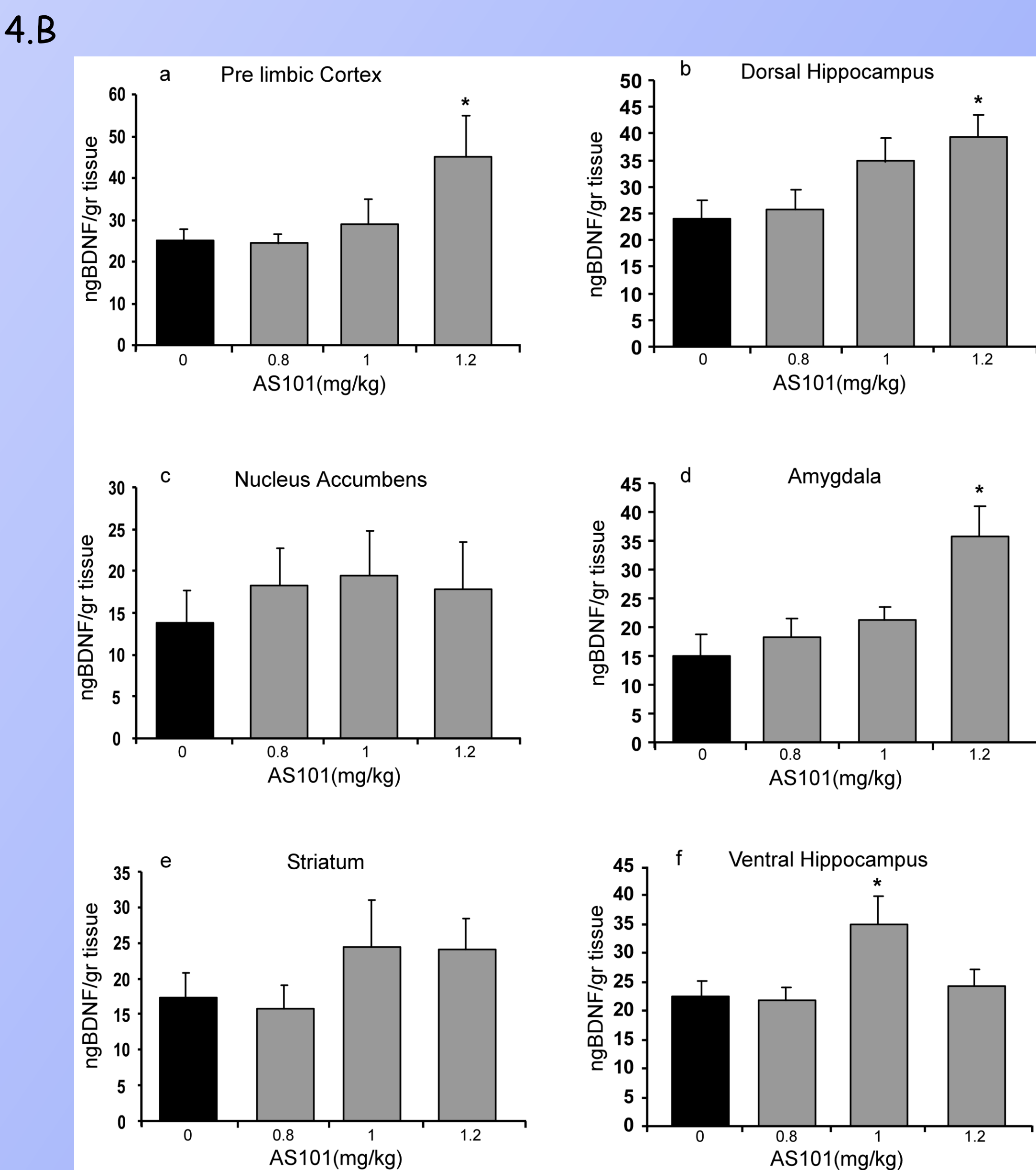
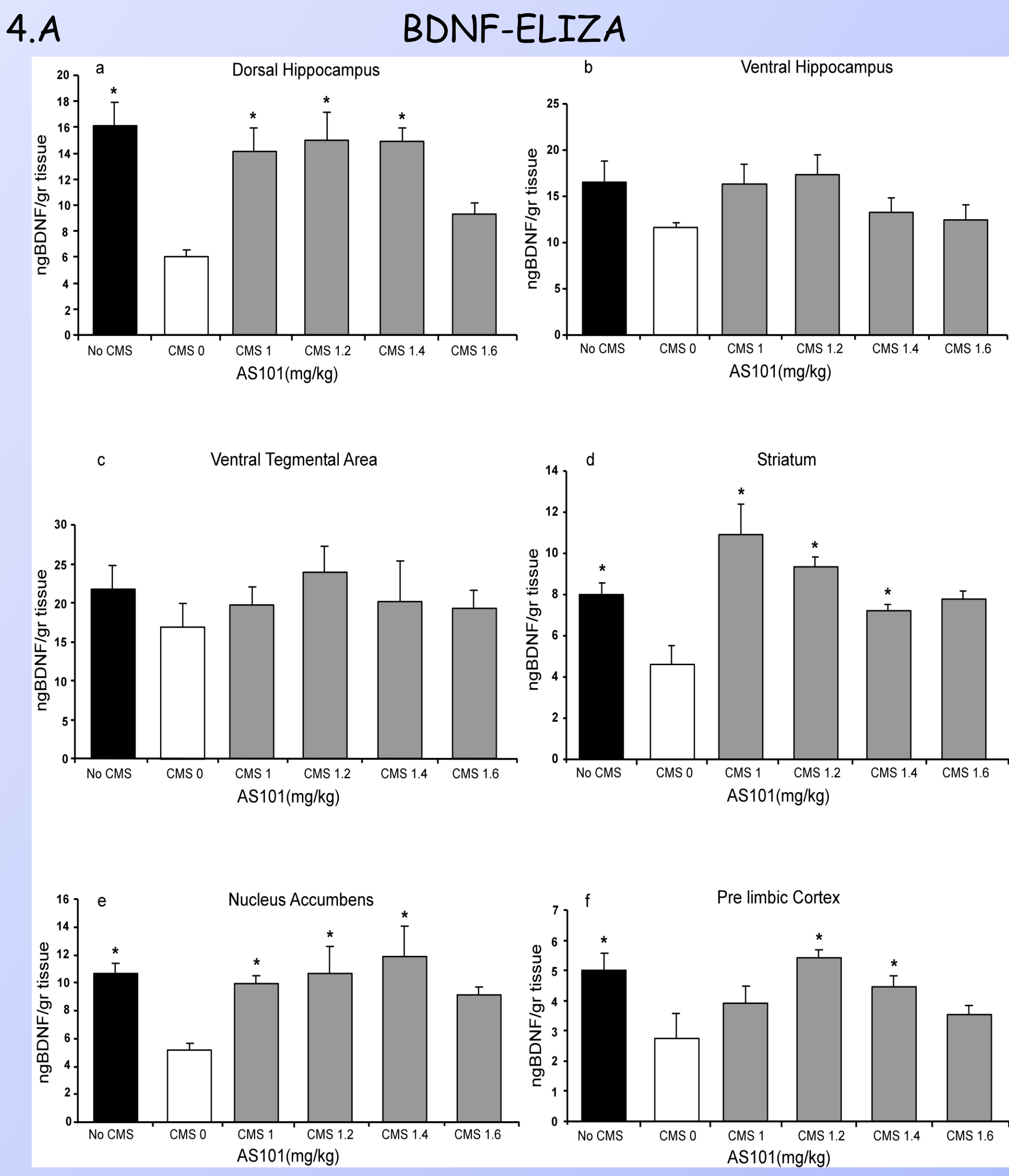


Fig 5. Specific doses of AS101, in the CMS model, effect P-GluR1 but not GluR1 protein expression in the dorsal hippocampus area. Data are presented as P-GluR1 (B) and GluR1 (C) normalized to Actin levels. \*p<0.05 for AS101 treatment VS CMS group

### Summary of results:

- AS101 increased sucrose preference, FST activity, and center visits in the exploration paradigm after CMS exposure and in animals from the DRL.
- AS101 up regulated BDNF levels in reward related-brain areas both in the CMS treated animals and in animals from the DRL and increased P-GluR1 expression in the dorsal hippocampus, which were reduced by the CMS procedure.

### Discussion:

AS101 has a beneficial behavioral effect that was correlative to molecular findings; while CMS induced reduction of sucrose preference (interpreted as anhedonia) and center visits (suggesting increased anxiety), AS101 normalized these behaviors. Moreover, AS101 increased mobility in the FST suggesting enhanced motivation. Finally, while CMS reduced hippocampal BDNF and P-GluR1, AS101 up-regulated these proteins in several brain regions. Taken together, AS101 a synthetic compound with a proven safety profile in humans, might serve as a novel anti-depressive therapy.