Background

A synthetic retinoid Am80, which has also been used clinically for patients with APL, has been reported to affect the brain and neurons. Am80 significantly promotes recovery from motor dysfunction in rats with a spinal cord injury, and restores the time latency for entering the dark compartment in the passive avoidance test in rats with memory defects induced by scopolamine. Senescence-accelerated mouse (SAM), developed by selective inbreeding of the AKR/J strain, is generally used in the study of aging diseases. In particular, SAMP8 (P8), one of the senescence-prone series, has been proposed as a model for the study of learning and memory deficits, and shows an emotional disorder characterized by reduced anxiety-like behavior. In this study, we investigated whether Am80 improved low anxiety behavior in P8.

Methods

Ten male P8 and ten R1 (senescence-resistant) per group were used. Am80 was given in feed corresponding to 2 mg/kg/day for 1.5 months. The behavioral tests, open field test, light and dark box test, hole-board test, and elevated platform test were performed at the age of 7–8 months. Immunohistochemical analysis was carried out for serotonin transporter (HTT), tyrosine hydroxylase, and dopamine transporter in sagittal or coronal brain sections. Monoamines (NE, DA and 5-HT) and their metabolites (MHPG, DOPAC, 3-MT, HVA and 5-HIAA) were measured in the cingulate gyrus, amygdala, and hypothalamus.

Results

In the open-field and hole-board tests, the number of ambulations, rearing, and head dipping, and the distance moved in P8 significantly increased compared to in R1, and in the light and dark box test, the latencies to the first exit in P8 significantly decreased compared to in R1, suggesting the low-anxiety condition in P8. In Am80-treated P8, these behavioral endpoints as emotion has restored retuned to the same level as those in R1. In the elevated platform test, the freezing time in Am80-treated P8 tended to be longer than in P8. The HTT-positive area in the coronal section of the forebrain of Am80-treated P8 increased compared to in P8. The 5-HT metabolic turnover in the amygdala, hypothalamus and cingulate gyrus of Am80-treated P8 increased compared to in P8. In both amygdala and hypothalamus, DA metabolic turnover in P8 was also improved by Am80 treatment.

Conclusion

Am80 improved low anxiety-like behavior in P8, which may be explained in part that Am80 increases monoamine metabolic turnover in P8. Retinoic acid seemed to show efficacy in learning and memory, especially through choline acetyltransferase (ChAT) induction because of the RAR response element in the transcriptional regulatory area of ChAT. In the present study, however, we showed for the first time that Am80 might directly or indirectly regulate monoamine, particularly the 5-HT system.