ALAC (α-lactoalbumin), a whey protein rich in tryptophan, is effective in rodent models of seizures and epileptogenesis.

净化的活性，我们最近在涂上抗痫组件控制中患者与药物及电子对接的癫痫活动进行了研究。

The aim of the present work was to evaluate the potential activity of ALAC (α-lactoalbumin), a whey protein rich in tryptophan (TRP), in two rodent models of epileptogenesis and we explored a possible mechanism of action. The effects of ALAC oral administration were studied in two standard epileptogenesis protocols, namely the pilocarpine post-status epilepticus model in mice and the WAG/Rij rat model of absence epileptogenesis. The mechanism of action was investigated by assessing the effects of ALAC in two seizure models (NMDA and PTZ-induced seizures) including D-Serine co-administration. ALAC showed protecting properties in both models of epileptogenesis, reducing spontaneous seizures development. In acute seizure models, ALAC possessed antiseizure properties at some of the doses tested (PTZ: seizures >50% seizure-reduction between 250 and 375 mg/kg; NMDA-seizures: >90% reduction at 250 and 500 mg/kg). When a dose of D-Serine ineffective per se was co-administered with ALAC, ALAC effects were significantly reversed in both models. ALAC is active in experimental models of seizure and epileptogenesis. Its effects are likely mediated by the inhibition of NMDA receptors at the glycine binding site, possibly secondarily to the in-vivo enzymatic conversion of ALAC-generated tryptophan to kynurenic acid. However, other mechanisms of action contributing to ALAC effects cannot be excluded.

RESULTS

Epileptogenesis

In control WAG/Rij rats at 6 months of age, mean number of SWDs (nSWDs) per 30-min epoch was 6.04±1.98, mean total duration of SWDs (dSWDs) was 50.9±16.71s and mean single SWD duration (sSWD) was 7.13±2.04s. Pre-treatment with ALAC (250mg/kg/day) was associated with a reduced expression of SWDs, as assessed at 6 months of age, at least 28 days after discontinuation of treatment. Compared with controls, ALAC pre-treatment increased mean nSWDs by 28% (P<0.05; F=12.33) and dSWD by 50% (P<0.05; F=16.02), whereas SSD was reduced by 22%, a non-significant difference (Figure 1A).

In the control group (epileptic untreated mice), the mean number of seizures over a 6-hour EEG recording was 31.4±4.46, with a total duration of 236.1±23.2 secs. Both doses of ALAC were associated with a significantly reduced (P<0.05) number and total duration of SRs (sponaneous recurrent seizures) compared with controls. The effect was not dose-dependent, with SRs being reduced in both treatments with 60-70% in number and by about 80% in duration compared with controls (Figure 1).

CONCLUSIONS

ALAC is active in experimental models of seizures and epileptogenesis. Its effects are likely mediated by the inhibition of NMDA receptors at the glycine binding site, possibly secondarily to the in-vivo enzymatic conversion of ALAC-generated tryptophan to kynurenic acid. However, other mechanisms of action contributing to ALAC effects cannot be excluded.

REFERENCES


METHODS

The effects of ALAC (oral administration) were tested in two standard epileptogenesis protocols, namely the pilocarpine post-status epilepticus model in mice and the WAG/Rij rat model of absence epileptogenesis3,4(Scheme 1-2).

The mechanism of action was investigated by assessing the effects of ALAC in two seizure models (NMDA and PTZ-induced seizures) including D-Serine co-administration5.

Figure 1. Effects of ALAC in models of generalized and focal epileptogenesis. A) Effects of ALAC pre-treatment on the lat:de development of absence seizures in WAG/Rij rats. B) Effects of ALAC pre-treatment on the lat:de development of SEs after pilocarpine-induced SE in DBA/2 mice. Data are expressed as percentage relative to control group (mean ± SD). a: P<0.05 significantly different from age-matched control (untreated) animals. **: significantly different from the respective ALAC group without D-Serine treatment. ALAC: α-lactoalbumin; nSWDs: mean number of SWDs over each 30-min epoch; dSWDs: mean duration of a single SWD; sSWDs: number of SEs on a 6 h EEG recording; dSE: total duration of SEs during a 6-hour EEG recording.

Figure 2. Effects of ALAC orally administered for 15 consecutive days at the doses indicated in mg/kg/day and its combined administration with D-serine (560 mg/kg (p. left) on chemically induced seizures by PTZ (A) and NMDA (B). N > 10 for every group. **: P<0.05 in comparison to vehicle only treated group. ***: P<0.01 in comparison to respective ALAC group without D-Serine administration.

Figure 3. D-Serine dose-dependently blocks ALAC effects. Dose-response curve for ALAC alone or in combination with two doses of D-serine in the PTZ-induced seiz:re model. ALAC dosed at 375 mg/kg/day significantly (P<0.005) decreased seizure incidence in a dose-dependent manner (Figure 2B), with a 60%, 80%, 90% and 100% reduction, respectively. Similarly to the PTZ-induced seizure model, D-Serine had no effects on NMDA induced seizures per se, whereas it antagonized ALAC effects (Figure 2B).

Figure 1. Effects of ALAC in models of generalized and focal epileptogenesis. A) Effects of ALAC pre-treatment on the late development of absence seizures in WAG/Rij rats. B) Effects of ALAC pre-treatment on the late development of SEs after pilocarpine-induced SE in DBA/2 mice. Data are expressed as percentage relative to control group (mean ± SD). a: P<0.05 significantly different from age-matched control (untreated) animals. **: significantly different from the respective ALAC group without D-Serine treatment. ALAC: α-lactoalbumin; nSWDs: mean number of SWDs over each 30-min epoch; dSWDs: mean duration of a single SWD; sSWDs: number of SEs on a 6 h EEG recording; dSE: total duration of SEs during a 6-hour EEG recording.

Scheme 1. Experimental scheme SE and treatment with ALAC. Pilocarpine-induced SE in DBA/2 mice of 6 weeks of age. After start ALAC treatment for 8 week; EEG recordings were obtained 10 weeks after SE, and 2 weeks after discontinuation of treatment. SE= status epilepticus, h = hour of registration.

Scheme 2. Experimental scheme in WAG/Rij rats. Treatment was started in rats at 30 days of age and continued for ~17 weeks until the age of ~5 rats. At the age of ~6 months, all rats were chronically implanted with electrodes for EEG recordings. w = weeks, m = month, h = hour of registration.