31ST ECNP CONGRESS
6-9 OCTOBER 2018
BARCELONA
P.677

Synergistic anticonvulsant effect of gidazepam and novel esters based on glycine and monoterpenes

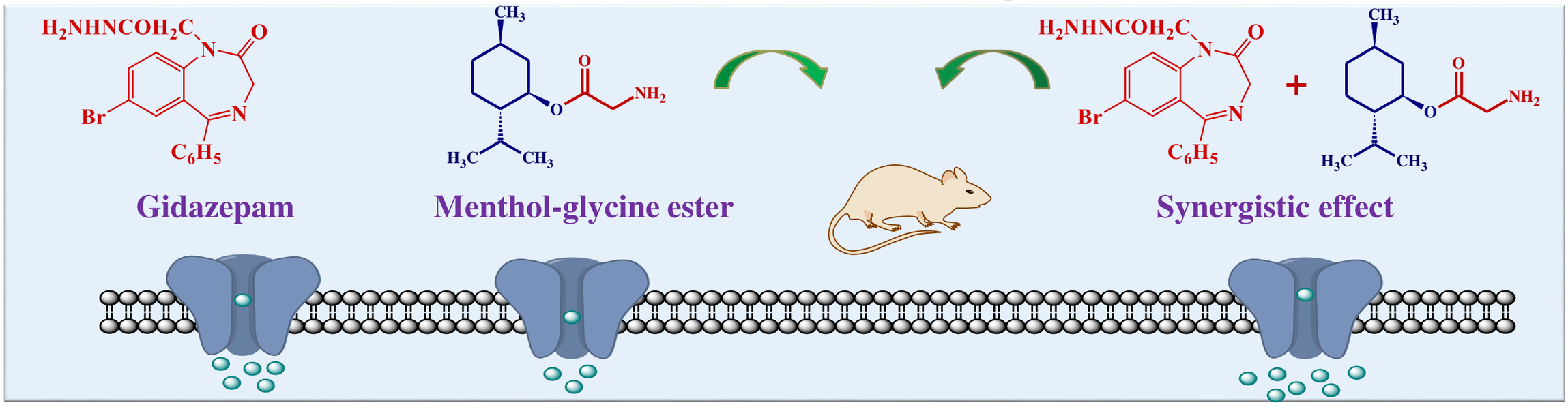
Mariia Nesterkina, Iryna Kravchenko

Odessa National Polytechnic University, Odessa, Ukraine
E-mail: mashaneutron@gmail.com, kravchenko.pharm@gmail.com

Background: Most commonly prescribed anticonvulsant drugs are able to alter CNS excitability by effecting GABAergic or glycinergic neurotransmission. Although GABA and glycine do not possess a significant antiseizure activity when administered themselves, they were found to potentiate the action of other anticonvulsants. Glycine, for example, potentiates the clinical effect of such anticonvulsants as phenytoin, phenobarbital and diazepam in DBA/2 audiogenic, 3-MPA and PTZ-induced seizures. At the same time, recent studies reported that cyclic monoterpenes such as menthol, thymol and others also have actions within the CNS and act as allosteric modulators of GABA(A) receptors whereas some terpenes are also antagonists of cortical glycine and GABA(A) receptors.

Objective: To investigate co-administration effect of gidazepam (GDZ) and novel esters based on glycine and monoterpenes – menthol, thymol, carvacrol, guaiacol, borneol and eugenol.

Methods: The experiment was carried out with outbreed male white mice distributed into 14 groups of five animals each, treated orally by: gidazepam (**GDZ**) 1 mg/kg (**1**); glycine ester of menthol 200 mg/kg (**2**); glycine ester of thymol 200 mg/kg (**3**); glycine ester of carvacrol 200 mg/kg (**4**); glycine ester of guaiacol 200 mg/kg (**5**); glycine ester of borneol 200 mg/kg (**6**); glycine ester of eugenol 200 mg/kg (**7**); mixtures of **GDZ** with each ester. The anticonvulsant activity of compounds **1**–**7** as well as mixtures of **1** with **2–7** was evaluated in model of acute generalized seizures induced by intravenous infusion of 1% pentylenetetrazole solution (PTZ) with the determination of PTZ minimum effective doses (MED) inducing clonic-tonic convulsions (CTC) and tonic extension (TE) in test animals. PTZ doses for inducing clonic-tonic convulsions (DCTC) and tonic extension (DTE) were calculated relative to control; pharmacological effect of compounds was estimated in 3 hours. All results are expressed as mean ± standard error mean (SEM).



Results: All esters of glycine with monoterpenes reveal antiseizure effect in 3 h after oral administration as evidenced by increasing of DCTC and DTE values. GDZ was found to protect against seizures with DCTC and DTE values of 181 and 191%, accordingly; whereas co-administration of GDZ and esters **2**–**7** was shown to increase anticonvulsant activity compared with each compound alone. It is noteworthy that glycine esters of alicyclic terpenoids **2** and **6** (menthol and borneol esters) combined with GDZ demonstrated the highest synergistic effect.

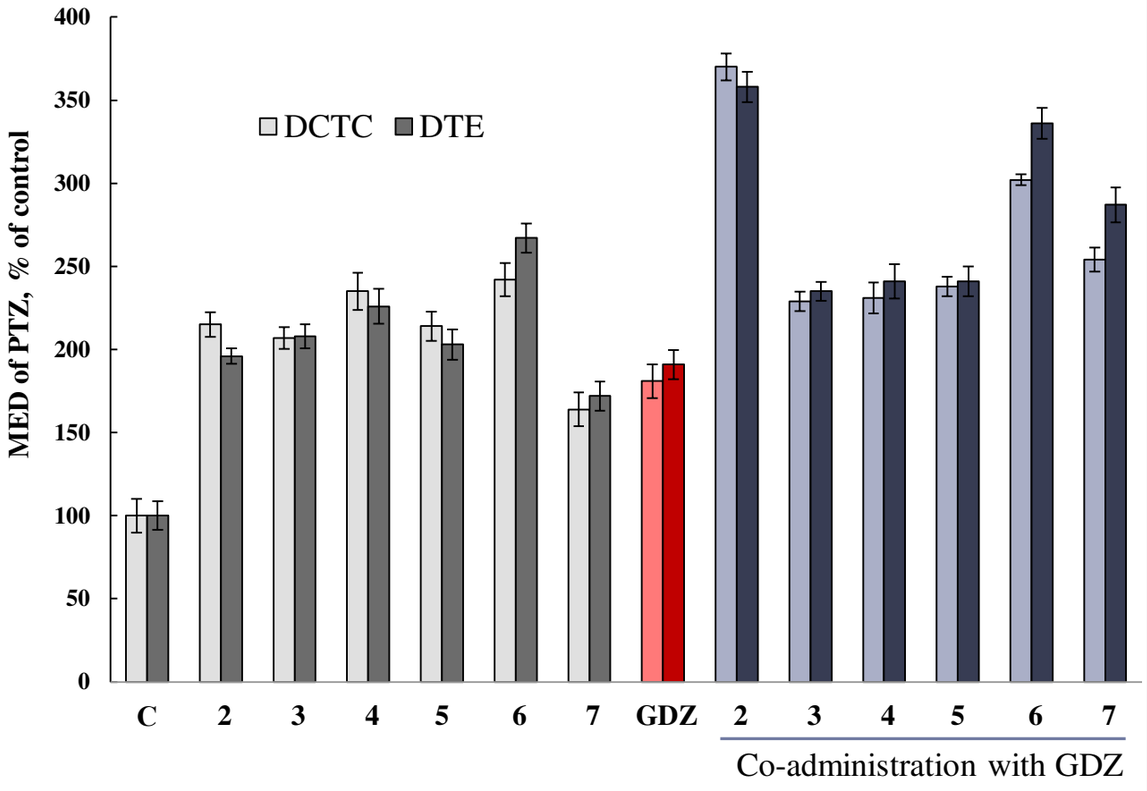


Figure. Anticonvulsant activity of compounds. C – control; GDZ – gidazepam.

Conclusion: Our experimental data demonstrate that orally co-administered gidazepam and glycine esters of monoterpenes produce synergistic effect in seizures prevention suggesting that these esters are not acting *via* the benzodiazepine site of GABA(A) receptors; these results are in agreement with those obtained by electrophysiological investigation.

DISCLOSURE: No potential conflict of interest