P.730

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The future of CNS treatments

ECNP neuroscience applied

Translocator protein 18 kDa may be responsible for anxiolytic effect modulation provoked by acute short-term stress in Balb/c mice

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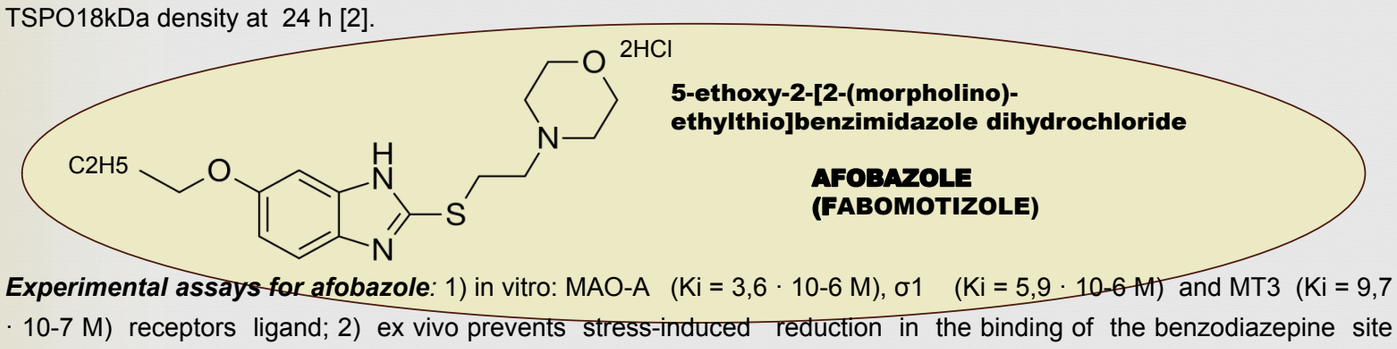
BACKGRAUND

Several studies have suggested that acute swim stress (ASS) alters the properties of benzodiazepines [1]. In the hippocampus, ASS caused a robust reduction in TSPO18kDa density 1 h after the stress and a distinct elevation in TSPO18kDa density at 24 h [2].



Experimental assays for afobazole: 1) in vitro: MAO-A (Ki = 3,6 · 10-6 M), σ1 (Ki = 5,9 · 10-6 M) and MT3 (Ki = 9,7 · 10-7 M) receptors ligand; 2) ex vivo prevents stress-induced reduction in the binding of the benzodiazepine site of the GABAa receptor, but attempts to determine binding sites on the GABAa receptor have produced negative results; 3) In vivo - selective anxiolytic effect in Balb/c but not in C57Bl/6 mouse, antidepressant-like effects in rats and mice, neuroprotective properties.

Clinical studies for afobazole: generalized anxiety disorders; neurasthenia; adaptation disorders, relief of withdrawal from smoking cessation.

It is assumed that afobazole and TSPO18kDa interactions can be the neurochemical events that lead to the restoration of the GABAa receptor function after emotional stress.

The aim of the study was to compare the TSPO18kDa function for behavioral effects of complete non-selective agonist GABAa receptor diazepam and MAO-A, σ1 and MT3 receptors ligand-like anxiolytic afobazole in "open field" test under ASS in male Balb/c mice.

METHODS

Male Balb/c mice (22–25 g) were housed at a constant temperature (22 °C), under a cycle of 12-h light/12-h darkness. The experimental groups were 8-10 mice each.

Behavioral responses (peripheral and central explorative activities, rearing, hole explorations) were recorded 15, 60 min or 24 h after a 10-min forced swimming procedure (in water t24-26©). Diazepam (1 mg/kg, 30 min before the tests), afobazole (1 mg/kg, 30 min before the tests), selective blocker TSPO18kDa PK11195 (1 or 5 mg/kg,60 min before the tests) or combinations of anxiolytics with PK11195 were administered intraperitoneally.

A single experiment was dealing with behavioral responses 15 min, 1 h or 24 h after acute stress without any pharmacological administrations.

Results are expressed as mean values ± S.E.M. Statistical analysis of results was by one-way ANOVA, followed by the Newman–Keuls multiple comparison test, and by two-way ANOVA, when the effects of two different treatments (stress, drug) were studied in the same experiment. The analyses were performed using Biostat v5.

Experimental Conditions	Substance administrations	Behavioral testing
NO STRESS*	Saline+Saline PK11195+Saline Saline+Diazepam PK11195+Diazepam	Saline+Saline PK11195+Saline Saline+Afobazole PK11195+Afobazole	2-min "open field" session
STRESS	Saline or PK11195 immediately after stress, 30 min after this and before testing - saline or anxiolytics	2-min "open field" session, 1h after stress
	Saline or PK11195 23h after stress, 30 min after this and before testing - saline or anxiolytics	2-min "open field" session, 24h after stress

* - Similar pharmacological combinations were applicable in stressed mice

RESULTS

In saline-injected mice, the explorative responses were suppressed 15 and 60 min after ASS (by 59% and 40%, respectively, p≤0.01) and increased – in 24 hours (by 33%, p≤0.05) compared with non-stressed mouse groups. In non-stressed mice, PK11195 reduced behavior by 75% (p≤0.05 compared with saline) and completely inhibited the central activities, while 24 hours after ASS RK11195 caused decrease of behavioral responses by only 37% (p≤0.05 compared with saline, p≤0.05 compared with PK11195 without ASS) without inhibiting activity in the center of experimental box. Diazepam effects were observed regardless of the period after ASS, while stress completely inhibited the afobazole effects 60 min later ASS, but not 24 h after ASS. In non-stressed mice, PK11195 completely suppressed the anxiolytic effect of afobazole while the PK11195 inhibiting effect was not observed 24 hours later ASS procedure. Diazepam effects did not depend on the TSPO18kDa function in non-stressed animals. However, 24 hours after ASS PK11195 weakened the diazepam effect by 30% (p≤0.05 compared with diazepam without ASS).

CONCLUSION

The results confirm the assumption the TSPO18kDa is one of the links in the mechanism of pharmacological effect changes induced by ASS. TSPO18kDa can be the way in which σ1-ligand afobazole prevents the stress-induced GABAa function attenuation.

[1] D. Peričić et al., Brain research. 2007, (1184): 81–7
[2] A. Avital et al., Neuropsyhopharmacology. 2001, 25(5):669-78

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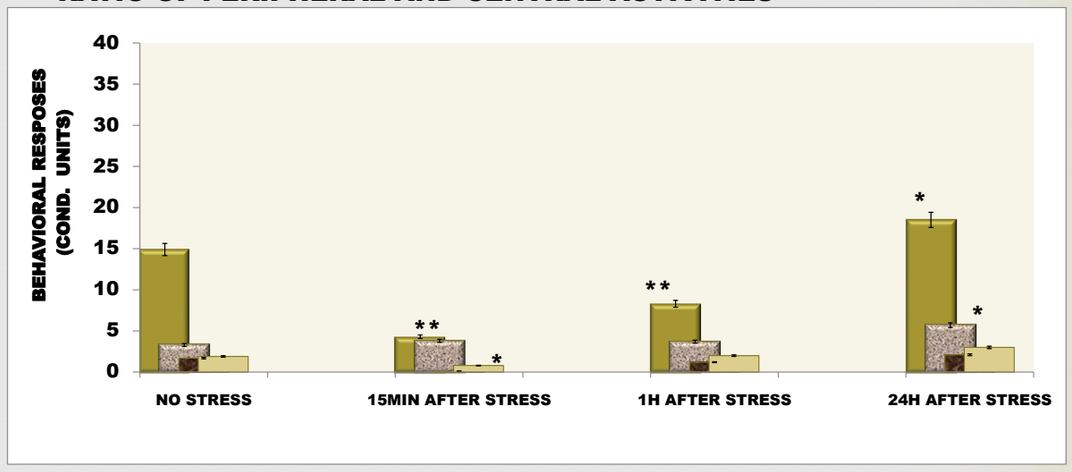
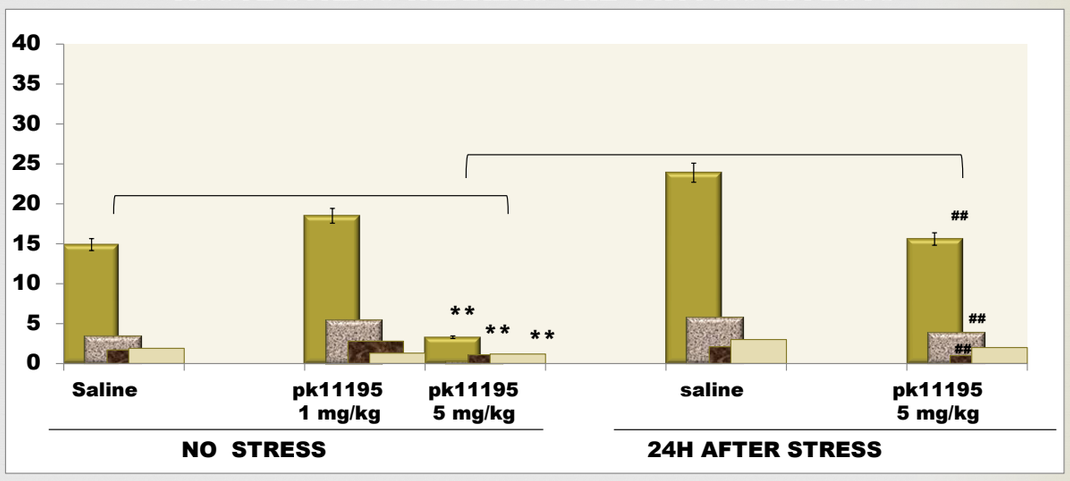
RESULTS

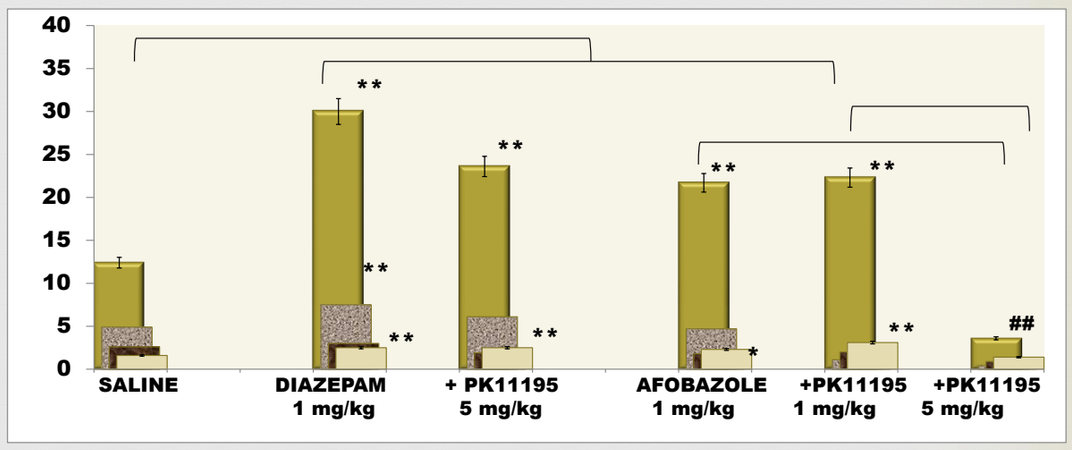
ACUTE STRESS AFFECTS THE HORIZONTAL ACTIVITY AND THE RATIO OF PERIPHERAL AND CENTRAL ACTIVITIES



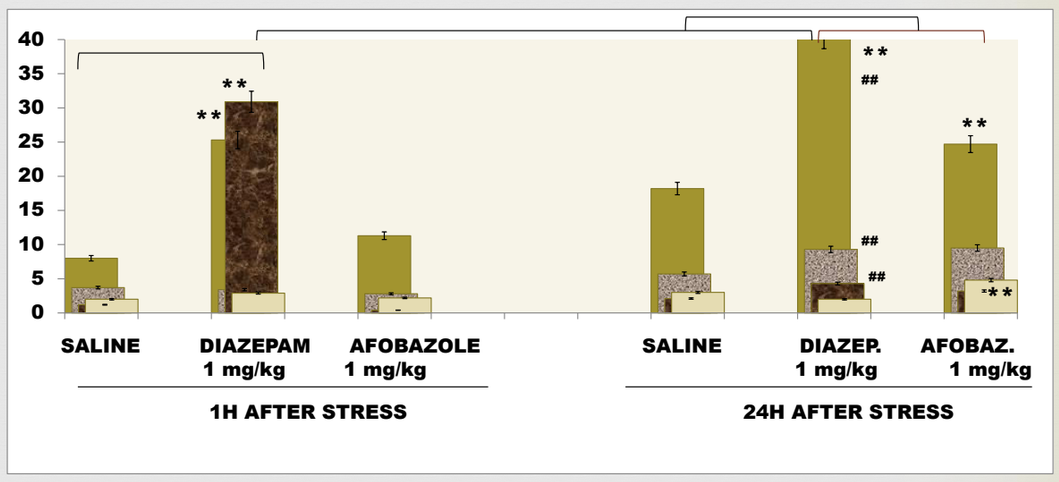
ACUTE STRESS WEAKENS THE PK11195 EFFECTS



PK11195 (5 MG/KG) INHIBITS THE BEHAVIORAL EFFECTS OF AFOBAZOLE IN NON-STRESSED MICE



TIME INTERVAL AFTER ACUTE STRESS DETERMINES THE BEHAVIORAL EFFECTS OF DIAZEPAM AND AFOBAZOLE



AT 24 H AFTER ACUTE STRESS, P11195 WEAKENS THE BEHAVIORAL EFFECTS OF DIAZEPAM, BUT NOT AFOBAZOLE