BMC Pharmacology

Meeting abstract

Benzodiazepines modulate $GABA_A$ receptors by reducing a gamma-subunit-mediated inhibition of GABA sensitivity

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from 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR) Joint meeting with the Hungarian Society of Experimental and Clinical Pharmacology (MFT) and the Slovenian Pharmacological Society (SDF)
Graz, Austria. 19-21 November 2009

Published: 12 November 2009

BMC Pharmacology 2009, **9**(Suppl 2):A23 doi:10.1186/1471-2210-9-S2-A23

This abstract is available from: http://www.biomedcentral.com/1471-2210/9/S2/A23

Background

Heterologous expression of α_1, β_2 and $\gamma_{2S}(\gamma_1)$ subunits produces a mixed population of $GABA_A$ receptors containing $\alpha_1\beta_2$ or $\alpha_1\beta_2\gamma_{2S}(\gamma_1)$ subunits. GABA sensitivity (lower in receptors containing γ_1 or γ_{2S} subunits) and the potentiation of GABA-activated chloride currents (I_{GABA}) by benzodiazepines (BZDs) are dependent on $\gamma_{2S}(\gamma_1)$ incorporation [1]. A variable γ subunit incorporation may affect the estimation of I_{GABA} potentiation by BZDs. We propose an approach for estimation of BZD efficiency that accounts for a mixed population of $\alpha_1\beta_2$ and $\alpha_1\beta_2\gamma_{2S}(\gamma_1)$ receptors.

Methods

We investigated the relation between GABA sensitivity (EC_{50}) and BZD modulation by analyzing triazolam-, clotiazepam- and midazolam-induced potentiation of I_{GABA} in *Xenopus* oocytes under two-microelectrode voltage clamp.

Results

Plotting EC_{50} versus BZD-induced shifts of GABA concentration-response curves (ΔEC_{50}(BZD)) of oocytes injected with different amounts of α_1, β_2 and $\gamma_{2S}(\gamma_1)$ cRNA (1:1:1-1:1:10) revealed a linear regression between $\gamma_{2S}(\gamma_1)$-mediated reduction of GABA sensitivity (EC_{50}) and ΔEC_{50}(BZD). The slope factors of the regression were always higher for oocytes expressing $\alpha_1\beta_2\gamma_1$ subunit receptors (triazolam: 1.8 ± 0.1; clotiazepam: 1.6 ± 0.1; midazolam: 2.3 ± 0.2) than for oocytes expressing $\alpha_1\beta_2\gamma_{2S}$ receptors (triazolam: 1.4 ± 0.1; clotiazepam: 1.4 ± 0.1; midazolam: 1.3 ± 0.1). Mutant $GABA_A$ receptors ($\alpha_1\beta_2$-R207Cγ_{2S}) with lower GABA sensitivity showed higher drug efficiencies (slope factors: triazolam: 1.1 ± 0.1; clotiazepam: 1.1 ± 0.1; midazolam: 1.2 ± 0.1) whereas higher GABA sensitivity of α_1-L263S$\beta_2\gamma_{2S}$ mutant receptors was associated with lower efficiency (slope factor: clotiazepam: 1.7 ± 0.1).

Conclusion

Regression analysis enabled the estimation of BZD efficiency when variable mixtures of $\alpha_1\beta_2$ and $\alpha_1\beta_2\gamma_{2S}(\gamma_1)$ receptors are expressed and provided new insights into the $\gamma_{2S}(\gamma_1)$ dependency of BZD action. The method for determining the slope of the regression line also allowed the determination of the percentage of $\alpha_1\beta_2\gamma_{2S}$ receptors. Assuming a twofold difference in the single channel conductance of $\alpha_1\beta_2$ and $\alpha_1\beta_2\gamma_{2S}$ receptors, at 70% current ratio of γ_{2S}-containig receptors our mathematical model predicts only about 50% of γ_{2S} subunit incorporation. Our data suggest that BZDs reduce a γ-subunit-mediated inhibition of GABA sensitivity.

Acknowledgements
This work was supported by FWF grant 15914 (SH).

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