Pharmacological Reports
2008, 60, 331–338
ISSN 1734-1140

Neonatal N-(-2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) treatment modifies the vulnerability to phenobarbital- and ethanol-evoked sedative-hypnotic effects in adult rats

Aleksandra Bortel[1], Lucyna Słomian[1], Dariusz Nitka[1], Michał Świerszcz[1], Mirella Jaksz[1], Beata Adamus-Sitkiewicz[1], Przemysław Nowak[1], Jadwiga Jośko[2], Richard M. Kostrzewa[3], Ryszard Brus[1]

[1]Department of Pharmacology, Medical University of Silesia, H. Jordana 38, PL 41-808 Zabrze, Poland

[2]Department of Environmental Medicine and Epidemiology, Medical University of Silesia, H. Jordana 19, PL 41-808 Zabrze, Poland

[3]Department of Pharmacology, Quillen College of Medicine, East Tennessee State University, Johnson City, TN 37614, USA

Correspondence: Przemysław Nowak, e-mail: pnowak@sum.edu.pl

Abstract:
To study the influence of the central noradrenergic system on sensitivity to sedative-hypnotic effects mediated by the aminobutyric acid (GABA) system, intact rats were contrasted with rats in which noradrenergic nerves were largely destroyed shortly after birth with the neurotoxin DSP-4 [N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine; 50 mg/kg *sc* x2, P1 and P3]. At 10 weeks, loss of the righting reflex (LORR) was used as an index to study the acute sedative-hypnotic effects of phenobarbital (100 mg/kg *ip*) and ethanol (4 g/kg *ip*, 25% v/v). Additionally, GABA concentration in the medial prefrontal cortex (PFC), hippocampus, cerebellum and brainstem was estimated by an HPLC/ED method. Neonatal DSP-4 treatment diminished the sedative-hypnotic effects of both phenobarbital and ethanol in adult rats. While the endogenous GABA content in the PFC, hippocampus, brainstem and cerebellum of DSP-4-treated rats was not altered, phenobarbital significantly decreased GABA content of both intact and DSP-4-lesioned rats by ~40% in the hippocampus and by ~20% in other brain regions at 1 h. Ethanol reduced GABA content by ~15–30% but only in the hippocampus and brainstem of both intact and lesioned rats. These findings indicate that the noradrenergic system exerts a prominent influence on sedative-hypnotics acting *via* GABAergic systems in the brain without directly altering GABA levels in the brain.

Key words:
noradrenergic, lesion, phenobarbital, ethanol, GABA, rats