

## Evaluating the Anti-Hypoxic and Anti-Ischemic effects of some GABA-receptor mimetics in Brains of mice and rats

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**Introduction:** Cerebrovascular accident (CVA) in which cerebral hypoxia and ischemia happen is one of the most important causes of disability and mortality in adults, however, it is not treated properly yet. Since the main reason of neural death in this disease is the release of excitatory substances like glutamate, inhibition of neurons with GABA receptor mimetics may reverse the excitotoxicity. In this study, we investigated the anti-hypoxic and anti-ischemic effects of diazepam and phenobarbital (GABA-A allosterics) and baclofen (GABA-B agonist) in comparison to phenytoin (sodium channel blocker and positive control) and normal saline (negative control).

**Materials and Methods:** The mentioned medicines were injected intra-peritoneally to mice in different doses before the hypoxia. For inducing hypoxia, we put mice individually in a sealed glass container in presence of soda lime and recorded their survival time. In order to create ischemic stress in rats for histopathological evaluation of the hippocampus, we used four-vessel occlusion method. 15 minutes after the ischemic period, 0.6-1cc normal saline, phenytoin 50mg/kg, diazepam 10mg/kg and phenobarbital 40mg/kg were then administered into the rats' peritoneums.

**Results:** There was a significant increase in the survival time of mice receiving 2mg/kg ( $PV < 0.01$ ), 5mg/kg, 10mg/kg, 15mg/kg ( $PV < 0.001$ ) of diazepam, 40mg/kg ( $PV < 0.01$ ) and 60mg/kg ( $PV < 0.001$ ) of phenobarbital, and 10mg/kg, 20mg/kg, 30mg/kg and 40mg/kg of baclofen ( $PV < 0.001$ ) compared to the negative control group ( $23.03 \pm 0.78$  minutes), while, the figure for phenytoin 100mg/kg (positive control) was  $55.3 \pm 3.21$  minutes ( $PV < 0.001$ ). Based on histopathologic examinations, diazepam had no noticeable anti-ischemic effect, however, the preventive effects of phenytoin and phenobarbital was prominent in comparison to the control group.

**Conclusion:** This study reveals that these compounds may be of great benefit in treating hypoxic-ischemic diseases of CNS.

Anxiety and restlessness are early symptoms of hypoxia; if hypoxia is not reversed, then hypotension will develop. A GABA receptor agonist is a drug that agonizes one or more of the GABA receptors, typically producing sedative effects, and can also cause other effects on the body, such as anxiolytic, anticonvulsant, and relaxation. There are three Gamma-Aminobutyric receptors in response to a cessation

or dose reduction of benzodiazepine, the number of GABA receptors is steadily restored. Treatment withdrawal rate needs to provide time for recovery of GABA receptors if withdrawal symptoms are to be reduced. "Brain is healing and rebalancing, but it takes time. GABA is binding on Receptor. GABA receptors are found in the post-synaptic membrane. When there are two molecules the receptor channel opens from the GABA bind to its receptor, and the chloride ions rush through the neuron. The GABA<sub>A</sub> receptor consists of five proteins in the subunits. GABA supplements are considered likely safe for up to 12 weeks when taken by mouth. However, pregnant and breastfeeding women should avoid GABA as there is insufficient information available to determine whether it is safe or effective. In comparison with its optical isomers and several selective monoamine inhibitors in mice, we assessed the anti-hypoxic and anti-ischemic actions of indeloxazine hydrochloride ((+/-)-2-[(inden-7-yloxy)methyl]morpholine hydrochloride, YM-08054) There was also Unlike traditional monoamine inhibitors, these effects of indeloxazine may be attributable, at least in part, to cerebral energy metabolism facilitation both serotonin and norepinephrine uptake, and its (+) -isomer, with an inhibitory action of serotonin uptake, increased the survival period of mice exposed to nitrogen gas and the gasping period in decapitated mice. Indeloxazine and its (+) -isomer have been about 3-10 times more potent than the (-)-isomer in terms of their anti-hypoxic and anti-ischemic activities. Selective norepinephrine inhibitors such as maprotiline and viloxazine and selective serotonin inhibitors such as citalopram, alaproclate, and zimeldine did not exhibit anti-hypoxic properties. On the other hand, amantadine, a selective dopamine inhibitor, and amitriptyline, a tricyclic antidepressant with anticholinergic properties, shortened the survival time significantly in on hypoxic mouse. In biochemical studies, increases in brain ATP and glucose levels were observed without affecting lactate levels in mice, and an increase in local use of cerebral glucose in 10 brain regions involving frontal cortex in rats following in deloxazine administration. These findings indicate that in deloxazine and its optical isomers have anti-hypoxic and anti-ischemic actions unlike traditional monoamine inhibitors, these effects of in deloxazine can, at least in part, be attributable to the facilitation of cerebral energy metabolism.