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MEETING ABSTRACT

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Neuroprotective action of gammapyrone, a GABA-containing peptide-mimicking compound

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A decrease in gamma-aminobutyric acid (GABA) system inhibitory activity is closely associated with the progression of Alzheimer's disease (AD) [1]. Deficiency in GABAergic signaling potentiates neuroinflammation, early hallmark of AD [2]. Gammapyrone (GMP) is a 1,4-dihydropyridine (DHP) compound containing one "free" and one "crypto" (incorporated into DHP cycle) GABA molecule joined via a peptide bond, thus creating a peptide-mimicking compound [3]. GMP, an atypical DHP, does not block neuronal calcium channels, but in a dose of 0.05 mg/kg demonstrated memory facilitation in naïve rats exposed to conditioned avoidance response test [4]. We suggested that in early AD-type model rats GMP may show spatial memory facilitation and normalize cell neurotransmitter balance.

We determined binding affinity of GMP for $GABA_{A1}$ (α1β2γ2) and $GABA_B$ receptors by using [^{3}H]muscimol and [^{3}H]CGP 54626, respectively. AD-type model rats (280 ± 20 g) were obtained by intracerebroventricular injection of streptozotocin (STZ, 750 µg/10 µl). All animals were treated intraperitoneally with saline (control) or GMP (0.01 and 0.05 mg/kg). Two weeks after STZ administration, locomotor activity and spatial learning/memory performance were assessed in the open field and water maze tests, respectively. Cortical and hippocampal expression was assayed immunohistochemically for astrocyte marker glial fibrillary acidic protein (GFAP), neuronal survival marker calbindin (CB), GABA-synthesizing glutamate decarboxylase-67 (GAD67) and acetylcholine-cleaving acetylcholinesterase (AChE). The expression of dopamine-synthesizing tyrosine hydroxylase (TH) was detected in the substantia nigra.

GMP demonstrated very low binding affinity for both $GABA_A$ and $GABA_B$ receptors. STZ administration produced deficits in spatial learning/memory in the water maze test, not influencing locomotion. STZ also induced remarkable neuroinflammation (astrogliosis), increase in AChE expression and slight decrease in GAD67 expression.

Both doses in STZ-treated rats significantly improved spatial learning/memory, protected against neuroinflammation, decreased acetylcholine cleavage. In the smallest dose GMP normalized cortical GAD67 expression while it did not bind to GABA receptors. CB and TH expression was not influenced by either STZ or GMP.

We conclude that the GABA-containing compound GMP provides neuroprotection in early AD-type model rats by targeting neuroinflammation, reducing acetylcholine cleavage, and cortical GABA, while not binding to GABA receptors. One may suggest that GMP action is provided via non-specific allosteric mechanisms. The neuroprotective activity of GMP indicates its putative usefulness in early stages of AD also in human beings.

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Keywords: GABA – gammapyrone (GMP) – streptozotocin – memory – neuroinflammation

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