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Review

Atypical 1,4-dihydropyridine derivatives, an approach to neuroprotection and memory enhancement

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ABSTRACT

This mini review is devoted to the design and pharmacological studies of novel atypical 1,4-dihydropyridine (DHP) derivatives which differ to a great extent from the traditional DHPs either by lack of neuronal calcium channel blocking activity and/or inability to protect mitochondrial processes. About 100 new DHP derivatives were screened and the mostly active were selected for detailed studies. The compounds of the series of the amino acid ("free" plus "crypto")-containing DHPs and lipophilic di-cyclic DHPs demonstrated long-lasting neuroprotective and/or memory-enhancing action, particularly at low doses (0.005–0.05 mg/kg) in different neurodeficiency rat or mice models, and exerted neurotransmitter-modulating effects. The studies have shown an ability of these atypical DHPs to normalize the expression of neuronal proteins, which participate in the regulation of neurotransmission (particularly of the GABAergic system) and synaptic plasticity that has been impaired in animal models, including Alzheimer's disease transgenic mice. The obtained results indicate that the tested DHP compounds can be considered as candidate molecules either for their further chemical modifications or for the more detailed studies to identify cell targets essential for neuroprotection and memory enhancing.

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1. Introduction

Compounds related to the 1,4-dihydropyridine (DHP) class have been intensively synthesized and pharmacologically studied since the early 1970s. The mechanism of action of most DHPs is to block calcium channels. This has resulted in the discovery of novel anti-hypertensive and anti-anginal drugs and the subsequent development of a wide range of well-known cardiovascular drugs, beginning from those of the first generation (e.g., nifedipine) to the second and third generation (e.g., amlodipine, isradipine, lercanidipine). The structure element of these drugs – the DHP cycle – can be regarded as a model compound of the redox coenzyme NAD(P)H or as an analogue of 1,4-dihydronicotinic amide. Therefore, DHPs have the ability to regulate redox reactions, possess free radical-scavenging properties, inhibit the peroxidation processes and protect biological membranes (for review, Ref. [1]). These effects and calcium antagonistic activity of the DHP backbone as the common structural feature were the basis to discover a wide spectrum of DHP derivatives as multifunctional regulators not only at the cardiovascular level, but also in the central nervous system, exerting anticonvulsant [2], analgesic [3], memory-enhancing [4] effects. Due to regulatory action of intracellular events other many – antibacterial, anticancer [5], hypoglycemic [6], and antimutagenic [3] properties have also been found, thereby indicating a

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promising trend for developing new drug candidates for the treatment of different disorders.

In addition, the DHP ring, which has been considered to be a crucial moiety for voltage-gated calcium channel modulatory properties [7] was shown also to interact with discrete receptor sites on the channel, which in turn are linked in complex allosteric relationships to other structurally quite distinct sites. Thus, DHP has become recognized as a versatile pharmacological template or privileged structure that can act as a molecular chameleon and exert potent actions not only on voltage-gated ion channels (L-, T-, and N-type of calcium channels, potassium channels) but also on receptors and enzymes [8]. Certainly, the interest to design new DHP is still unremitting in this millennium. One of novel approaches is to find selective voltage-gated calcium channel L-type (LTCC) $Ca_V1.3$ subtype antagonists, suggesting that this subtype predominantly is expressed in the brain tissue and therefore may exert high neuroprotective activity [9]. The novel compound 5-unsubstituted 6-aryl 1,4-DHP was tested in vitro and showed good activities in acute ischemia/reperfusion models of oxygen and glucose deprivation [9]. There is also continuation to find new structures of DHP derivatives, for instance, synthesis of benzodiazepine-dihydropyridine hybrid molecule JM-20, in which benzodiazepine portion is covalently linked to the DHP ring, and which prevented PC-12 cell death induced either by glutamate, hydrogen peroxide or KCN-mediated chemical hypoxia, as well as showed mitochondria protecting action [10]. Unfortunately we have not found *in vivo* data of the neuroprotective and memory-enhancing activities of these novel compounds.

In Latvia, the synthesis of novel DHP derivatives as antihypertensive agents was started at the Latvian Institute of Organic Synthesis, Laboratory of Membrane Active Compounds (Head Prof. Gunars Duburs) since the 1980s. A good cooperation between chemists and pharmacologists (who later moved to the University of Latvia) have produced considerable data also concerning the influence of novel DHPs on functions of the central nervous system (CNS). This mini review shows an insight in some most active DHP derivatives (Fig. 1) selected from about 100 screened compounds and studied since the 1990s, and is focused on novel type – atypical DHPs which having no typical neuronal calcium channel blocking and/or mitochondria-protecting action, possessed even higher and longer memory-improving activity in comparison to those of typical and well-described DHPs.

2. Monocyclic amino acid-containing DHPs (glutapyrone, tauropyrone)

The design of novel type of DHPs was started with adding of "free" amino acid (glutamate, taurine, GABA, or alanine) residue to the DHP ring at position 4 (instead of phenyl group which was typical moiety for classical DHPs). In addition, we found that amino acid elements (e.g. GABA, glutamate, beta-alanine, or NMDA) are incorporated into the DHP cycle and called them as "crypto" amino acids. Both the "free" and "crypto" amino acids were joined via the peptide bond (-CONH-), thus forming dipeptide-mimicking or pseudo-dipeptide compound. "Crypto" amino acids can be considered also as the cyclic unsaturated amino acids, and some examples of them are given in chemical article [11]. We expected that these peptide-mimicking monocyclic DHP structures will show effects similar to peptides by acting at low doses/concentrations and by regulation/normalization of brain neurotransmitter activities and behaviour.

Depending on "free" amino acid moiety the compounds were named as glutapyrone, tauropyrone, gammapyrone, alapyrone. Among 12 amino acid-containg DHPs the most studied were the glutamate-containing glutapyrone ([2-(2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine-4-carboxamido)-glutaric acid disodium salt]) and the taurine-containing tauropyrone [2-(2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine-4-carbox-amido)-ethansulfo acid sodium salt]. Fig. 2 shows general structure of amino acid-containing DHPs with "crypto" GABA. First pharmacological studies showed that the action of monocyclic DHPs differed qualitatively and quantitatively from those of typical di-cyclic (phenyl-DHP) compounds by lack of the calcium channel antagonizing properties (up to 100 μM) in neuronal synaptosomes [12,13] and myocardial slices [14]. They lacked also binding ability to the DHP receptor sites, showed high solubility, did not exert an influence on hemodynamics, and showed an extremely low toxicity: LD50 >8 g/kg i.p versus approximately 200 mg/kg for typical DHPs in mice [15].

The peptide-like action of amino acid-containing DHPs was clearly seen in different neurodeficiency animal models in which the compounds demonstrated neuroprotective properties and learning/memory improving activity (conditioned and passive avoidance tests) in rats at low doses, particularly of 0.005 and 0.05 mg/kg i.p. [15,16] that have not previously been described for traditional DHPs (used at 5–20 mg/kg). In addition, the protective action was long-lasting, even for months. For instance, glutapyrone administration in off-springs (on postnatal days 7–17) of previously maternally alcoholised rats (in gestation period) considerably improved memory in conditioned avoidance response test when the rats have been reached adulthood [16]. This was also shown for tauropyrone [17]. Another argument in favour to peptidomimetic action of these compounds is a lack of strict dose-response relationships and rapid reaching of the plateau state.

Studies of the mechanisms of action of the amino acid-containing DHPs showed neuromodulatory effects at the level of different neurotransmitter systems, having no direct binding to receptors. For instance, glutapyrone did not bind to NMDA- or non-NMDA receptors, while it (also tauropyrone) protected (at 1, 10 and 100 μM) rat cerebellar granule cells against glutamate excitoxicity and from oxygen-glucose deprivation-induced ischemia/hypoxia and cell damage (increase in lactate dehydrogenase level) [18,19]. Tauropyrone, which shortened ethanol-sleeping time in rats did not display binding activity to either GABA-A or GABA-B receptors [20], probably may indirectly interact with ethanol-sensitive sites either at the level of the GABA-A receptor modulatory site or at other, non-GABA receptor proteins or channels. In different routine convulsion tests by use of pentylenetetrazole [13] or bicuculline and thiosemicarbazide [21] glutapyrone demonstrated anti-convulsant properties indicating restoration of GABAergic processes. The multi-regulating profile of glutapyrone under pathological conditions was assumed also from immobilization stress studies wherein glutapyrone completely restored both the inhibitory GABA and the excitatory neurotransmitter noradrenaline levels in the hypothalamus and the striatum [22]. This type of multifaceted regulation is well-known feature of neuropeptides.

The influence of amino acid-containing DHPs on intracellular processes is only partially understood. For instance, they unlike typical di-cyclic DHPs which demonstrate a considerable mitoprotecting activity [23] were unable to protect rat cerebellar granule cells against MPP^+-induced cell death, the production of reactive oxygen species or the loss of mitochondrial membrane potential [24]. The mitochondria-protective activity was no found also in rat isolated liver mitochondria [25]. However in an azidothymidine (an inhibitor of mitochondrial complex I) toxicity model in mice, glutapyrone (1 mg/kg) acted as an anti-inflammatory/anti-apoptotic agent by regulating the azidothymidine-induced overexpression of proteins which are related to neuroinflammation and apoptosis—NF-κBp65 and caspase-3 [26]. Tauropyrone (1 mg/kg) showed a dual action in the brain: per se it demonstrated pro-