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Genotoxic and genoprotective effects of 1,4-dihydropyridine derivatives: a brief review

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This review summarises current knowledge about the genotoxic and genoprotective effects of 1,4-dihydropyridines (DHP) with the main focus on the water-soluble 1,4-DHPs. Most of these water-soluble compounds manifest very low calcium channel blocking activity, which is considered "unusual" for 1,4-DHPs. Glutapyrone, diludine, and AV-153 decrease spontaneous mutagenesis and frequency of mutations induced by chemical mutagens. AV-153, glutapyrone, and carbatones protect DNA against the damage produced by hydrogen peroxide, radiation, and peroxynitrite. The ability of these molecules to bind to the DNA may not be the only mechanism of DNA protection, as other mechanisms such as radical scavenging or binding to other genotoxic compounds may take place and enhance DNA repair. These uncertainties and reports of high 1,4-DHP concentrations damaging the DNA call for further *in vitro* and *in vivo* preclinical research, pharmacokinetic in particular, as it can help pinpoint the exact mechanism(s) of the genotoxic and/or genoprotective action of 1,4-DHPs.

KEY WORDS: 1,4-DHP; AV-153; diludine; DNA binding; carbatones; glutapyrone

Synthetic derivatives of 1,4-dihydropyridine (1,4-DHPs, Figure 1) produce various important biochemical and pharmacological effects (1), which are mainly owed to the blocking of calcium channels with subsequent modulation of different intracellular pathways. However, not all 1,4-DHPs are calcium antagonists, and some of their effects are owed to alternative mechanisms such as direct scavenging of free radicals (2), protection against mutagens, and activation of DNA repair (3). Some of these 1,4-DHPs have genoprotective properties (3–5) and others are genotoxic (6). The aim of this brief review is to summarise literature data on the genoprotective and genotoxic activities of these 1,4-DHPs. We relied on our own studies and those indexed in the PubMed database.

ANTI- OR PRO-OXIDANT PROPERTIES OF 1,4-DHPs

Many 1,4-DHPs have a significant ability to donate hydrogen and electrons and participate in redox reactions. Like ascorbic acid and tocopherols, they have been reported dual anti- and pro-oxidant effects, depending on their structure and reaction conditions (7).

1,4-DHP derivatives can scavenge nitric oxide (8), alkyl, alkyl peroxy radicals, and the 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical cation (2, 9, 10). In our earlier research (11–13) our group tested 1,4-DHPs for peroxynitrite- and hydroxy radical-scavenging potential, which singled out cerebrocrast, etaftorone, fenoftorone, and some 2,6-dimethyl-3,5-diethoxycarbonyl-4-(Na carboxylate)-1,4-dihydropyridine (AV-153) salts as efficient peroxynitrite scavengers, whereas hydroxy radical scavenging turned out to be modest (Table 1). Considering that many of these compounds manifest DNA-protective effects in living cells (see below), it is reasonable to assume that these effects are not owed to peroxynitrite and hydroxy radical scavenging or that these interactions play a minor role. On the other hand, AV-153-Na, AV-154-Na, and carbatone have a rather high scavenging capacity for oxygene radicals. In the human osteosarcoma cell line (HOS), AV-153-Na and carbatone lowered free radical production caused by hydrogen peroxide if pre-incubated with the HOS cells but were not effective if administered to those already treated with H_2O_2 (14). Pre-treatment with AV-153-Na, AV-154-Na, and carbatone showed a concentration-dependent, bell-shaped curve of protective effects, that is, they generally improved as the applied concentrations reached the middle range of 250 to 500 μmol/L, after which ROS levels increased (14). Milkovic et al. (14) also reported an interesting finding that 1,4-DHPs increased glutathione levels, which was an indirect antioxidative effect.

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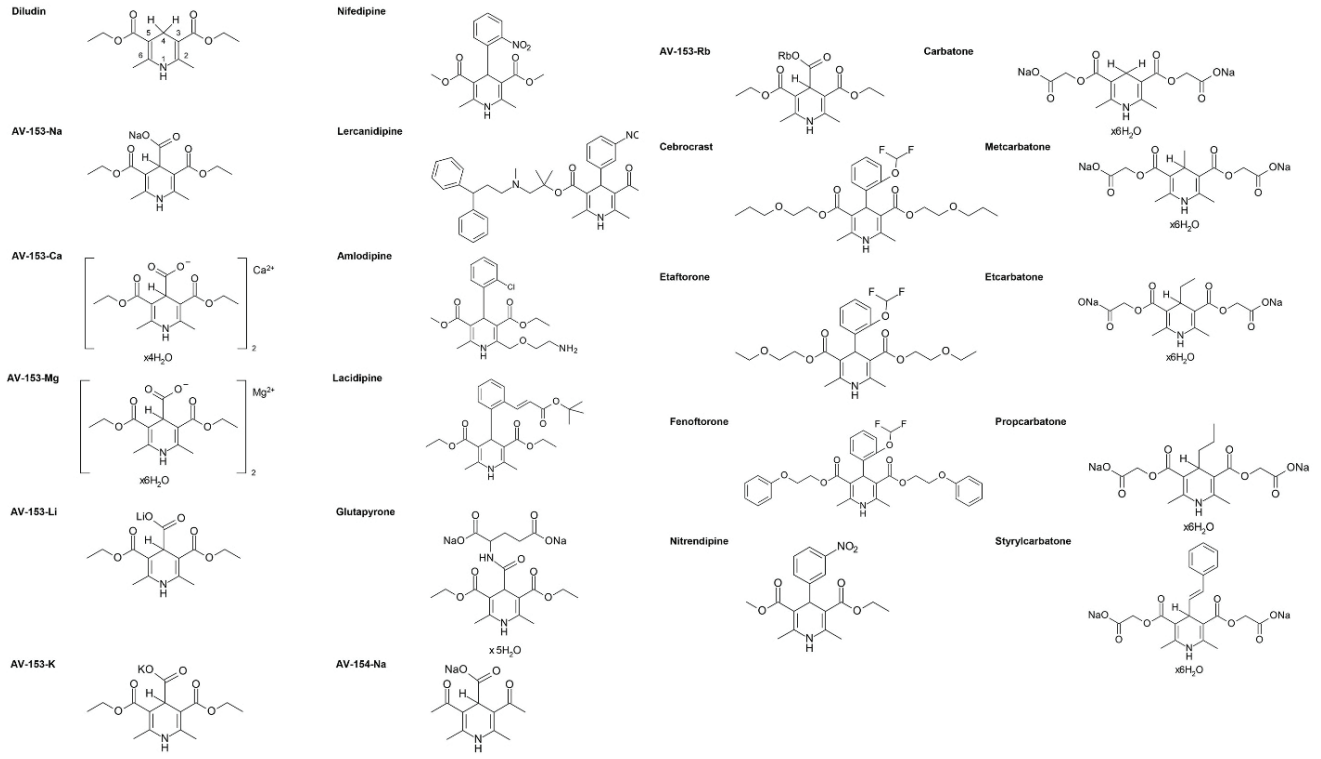

Figure 1 Chemical structure of 1,4-DHP derivatives included in this review

In vitro molecular interactions and DNA binding

Testing for 1,4-DHP effects in simple systems such as plasmid can reveal some interesting properties of 1,4-DHPs. Plasmid relaxation, which is indicative of DNA strand breaks, has been reported with some novel 1,4-DHP derivatives containing halogen atoms and/or nitro groups. Moreover, these compounds competed with restrictases for their binding sites (6). One of our earlier studies (13) singled out nitrendipine and AV-153-Ca and AV-153-Mg as the best DNA protectors, followed by etcarbatone and styrylcarbatone (Figure 2, previously unpublished). The effect was not concentration-dependent. In another study (15), we showed that etaftorone, fenoftorone, and cerebrocrast protected plasmid DNA against peroxynitrite-induced damage. At that point, it was believed that cerebrocrast, a lipid-soluble 1,4-DHP derivative with promising antidiabetic and neuroprotective activities but very weak Ca-channel blocking, and its analogue etaftorone act mainly on mitochondria (16–18), but both compounds turned out to be DNA binders (15).

The ability of 1,4-DHPs to bind to the DNA was first reported as early as in 1975 (19), suggesting an intercalative mode of DNA binding on the example of diludine and its analogues, but this research was discontinued. Diludine and its methylated analogue were shown to increase the melting temperature of DNA by 2.9 and 1.4 °C, respectively. One of our studies (20) called the attention to the DNA-binding capacity of antimutagenic AV-153-Na, as the docking experiment predicted its insertion in the DNA molecule at the place of a single-strand break, and the prediction was proven experimentally, as AV-153-Na forced ethidium bromide out of the DNA complex and showed higher affinity to damaged DNA than the intact molecule. Another, more recent study (12) has shown that DNA-binding capacity and DNA protection depend on metal ions forming salts with the AV-153 residue. In it, the fluorescence assay showed that the binding affinity dropped with each metal in the following order: Mg>Na>Ca>Li>Rb>K. Later use of spectroscopic and electrochemical methods has suggested intercalation as the main mode of action, although other types of interaction are also possible (21).

Another group of water-soluble 1,4-DHPs, i.e. carbatonides, disodium-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(carbonyloxyacetate) derivatives, including carbatone, metcarbatone, etcarbatone, and styrylcarbatone have also been reported to interact with DNA but to have a lower affinity for DNA than AV-153 salts. Among them, styrylacarbatone had the highest affinity and suggested a different binding mechanism (13). This and our another study (22) also suggest that the DNA-binding affinity of water-soluble monocyclic 1,4-dihydropyridine derivatives with a carboxylate group in position 4 depends on substituents in positions 3 and 5.

We also demonstrated that 1,4-DHP derivatives, more specifically AV-153 salts, can bind to the G-quadruplexes (G4), with Na and K salts effectively binding to the human telomere repeat

Table 1 Comparison of some properties of studied 1,4-DHP derivatives (11, 12, 15, 20, 25)

1,4-DHP derivative	DNA binding constant (UV/VIS spectroscopy) (M^{-1})	Stern-Volmer binding constant (EtBr extrusion) (M^{-1})	DNA binding constant (spectrofluorimetry) (M^{-1})	Effect on hydroxyl radical production (EPR; %)	Peroxynitrite decomposition time compared to control	Decrease in DNA damage in HeLa cells by peroxynitrite after pre-incubation with 10 nmol/L of a 1,4-DHP (%)
AV-153-Na	$7.21328x10^4$	$9.4x10^4$	$4.40x10^5$	96.8	0.75	50
AV-153-Ca		$1.7x10^5$	$4.04x10^5$		3.44	57
AV-153-Mg		$2.3x10^5$	$5.43x10^5$		7.52	NS
AV-153-Li		$9.9x10^4$	$3.32x10^5$		3.48	NS
AV-153-K		$8.7x10^4$	$2.70x10^5$		3.13	19
AV-153-Rb		$8.9x10^4$	$3.07x10^5$		3.00	14
AV-154-Na	No binding			98.7	0.29	NS
Carbatone	$1.09x10^2$			100	N/A	
Metcarbatone	$0.82x10^2$		$3.8x10^2$	31.4		
Etcarbatone	$0.54x10^2$		$9.5x10^2$	98.3		
Propcarbatone	$1.11x10^2$			86.4		
Styrylcarbatone	$1.9x10^3$	?	$1.4x10^4$	106		
Glutapyrone	No binding					27
Cerebrocrast			$2.2x10^3$		8.61	29
Etaftorone					2.25	27*
Fenoftorone					2.28	

* at the concentration of 1 nmol/L. NA – not assayed; NS – not significant

(18). Other authors confirmed G-quadruplex binding with a series of other novel 1,4-DHP derivatives (23).

Another recent study (24) has shown that widely used 1,4-DHPs with Ca blocker activity such as nifedipine, lercanidipine, and amlodipine can bind to the minor groove of the DNA, yet their binding affinity is low.

Modification of gene and protein expression

One of our earlier studies (16) has shown that pre-incubation with AV-153-Na (50 nmol/L) protects the DNA of HeLa cells against damage produced by peroxynitrite (200 μmol/L), as AV-153-Na penetrates the cell nucleus and up-regulates DNA excision repair enzymes. We then tested different salts of AV-153 for protectective DNA effects to learn that they were modified by the metal ions (12). AV-153-Na and AV-153-Ca effectively reduced DNA damage, AV-153-K and AV-153-Rb were less effective, whereas AV-153-Li did not protect the DNA, and AV-153-Mg even increased the damage. The AV-153 Na salt decreased DNA damage in HeLa cells through the over-expression of the pro-apoptotic protein DUX4 (Figure 3, previously unpublished). In human B-lymphocytes AV-153 Na, K, Ca, and Mg salts reduced DNA damage produced by oxidative stress caused by incorporation of the HIV-derived Tat protein (12). In another study (25), we have also found that glutapyrone protects HeLa cells against peroxynitrite, but to a lower extent than AV-153-Na.

Lipid-soluble cerebrocrast and etaftorone also seem to alleviate peroxynitrite-induced DNA damage (15). Cerebrocrast (50–500 nmol/L) is effective when administered before or together with peroxynitrite, but etaftorone is effective only when given at the same time.

1,4-DHPs AS DNA REPAIR ENHANCERS

Cell studies

In a study using single-cell gel electrophoresis (the comet assay) (4), AV-153-Na was reported to reduce the number of spontaneous DNA strand breaks in HL-60 human blood lymphocytes and Raji cells. It also reduced DNA damage produced by exposure to 2 Gy of gamma-radiation, 100 μmol/L ethylmethane sulphonate (EMS), or 100 μmol/L hydrogen peroxide by up to 87 % at AV-153-Na concentrations between 1 and 10 nmol/L. A later study (3) showed that AV-153-Na stimulated the synthesis of poly(ADP-ribose) in hydrogen peroxide-treated cells and that the short-term increase in the polymer's synthesis correlated with the higher rate and efficiency of DNA repair (3). In another study (5), AV-153-Na also reduced the number of micronucleated and apoptotic cells in a culture of human lymphocytes exposed to 2 Gy gamma radiation. The authors suggested that this effect was owed to its similar structure with the

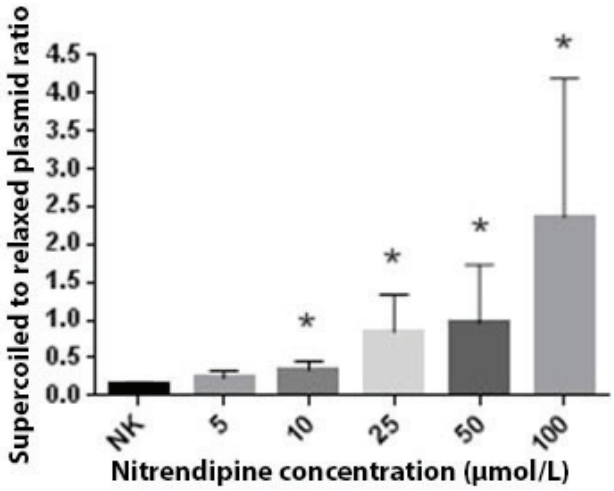

Figure 2 Protective effects of nitrendipine against pTZ57R DNA plasmid damage caused by Fenton reaction products. The pTZ57R DNA plasmid (1.4 μg) was incubated for 30 min with 0.003 % H_2O_2 in 0.01 mmol/L $FeSO_4$ with no or 5, 10, 25, 50 or 100 μmol/L nitrendipine And electrophoresed following the standard procedure. NK – negative control

nicotinic acid and its involvement in NAD^+ recovery and poly(ADP-ribosyl)ation (5). In a culture of Chinese hamster ovary cells (CHO-K1) treatment with AV-153-Na before exposure to X-rays did not affect the formation or repair of single-strand DNA breaks, but – judging by the FPG-modified comet assay – did prevent the formation of 8-oxoguanine (26).

Animal studies

When orally administered to laboratory rats (0.05 or 0.5 mg/kg) for three days, metcarbatone, etcarbatone, and styrylacarbatone caused damage to the DNA in nucleated blood cells. However, in animals with diabetes mellitus, metcarbatone and styrylcarbatone lowered DNA damage, whereas etcarbatone increased it (13). In our most recent (still unpublished) studies, oral AV-153-Na and glutapyrone also increased DNA damage in blood cells of control rats, but AV-153-Na did not significantly change the expression of the histone γ-H2AX in rat myocardium and mitigated the frequency of double-strand breaks. In another study using an experimental model of myocardial infarction (27), lacidipine decreased the level of 8-oxoguanine and therefore the DNA damage caused by oxidative stress.

Several studies using a rat streptozotocin-induced diabetes model looked into how 1,4-DHPs modify the expression of several genes and proteins involved in radical production and DNA repair (12, 15, 28). In most cases 1,4-DHPs increased the gene expression, which implies some level of influence on pathways regulating gene transcription. Other studies with diabetes mellitus have reported down-regulation of NO production and/or inducible NO synthase (iNOS) by carbatonides, etaftorone, fenoftorone, cerebrocrast (13) and AV-153 (29), which looks promising.

Antimutagenic and anticlastogenic action

The first findings about the effects of 1,4-DHP derivatives on spontaneous mutations were reported for *Drosophila melanogaster* in 1980 by Goncharova et al. (29). The larvae fed with diludine and AV-153 had a decrease in both point mutations and chromosome aberrations. The authors concluded that these mononuclear 1,4-DHPs were more efficient antimutagens than trinuclear compounds and that their antimutagenic efficiency was related to the presence of a carboxylate group in position 4.

Studies that followed reported AV-153-Na to reduce the frequency of genetic damage (point mutations and chromosome breakage) induced by EMS in *Drosophila melanogaster* larvae and imagoes more efficiently than standard radioprotectors cysteine and cysteamine (30). Similar protective effect against EMS-induced mutations was reported for glutapyrone in the spermatozoa of *Drosophila* pre-treated at the larval stage (31). Both compounds also showed an anticlastogenic effect in in mice (32), whereas glutapyrone was also reported for an antineoplastic effect in rats exposed to continual gamma irradiation (33).

Back to *Drosophila*, lipid-soluble 1,4-DHPs cerebrocast and diethone (diludine) also showed antimutagenic and anticlastogenic effects (34). More recently, diludine was shown to favour gamete storage in fish (35).

CONCLUSIONS

Considering the puzzling ability of 1,4-DHP derivatives to bind to the DNA, it would be important to establish the mechanisms by which they protect or damage the genome. Of course, this consideration should include their antioxidative potential, even though not all 1,4-DHPs seem to scavenge peroxynitrite or hydroxyl radicals. What we have learned so far is that some potent DNA binders, such as AV-153-Na and AV-153-Ca, produce stronger DNA-protective effects than the weak ones, such as AV-153-K and AV-153-Rb, yet some strong binders, such as AV-153-Mg and AV-153-Li, do not protect the DNA. Furthermore, glutapyrone, which is a weak binder, produces effects comparable to those of some strong DNA binders. All this suggests that DNA binding may not be the only mechanism of DNA protection, but may include radical scavenging or chemical binding of other genotoxic compounds. We also cannot exclude the possibility that some weak binders metabolise in the organism into strong binders. For example, glutapyrone easily metabolises to AV-153. Furthermore, even though DNA binding mobilise DNA repair enzymes, high concentrations of potent binders such as AV-153Na, Mg, or Li salts can damage the DNA.

All these considerations call for further testing of novel as well as clinically approved 1,4-DHPs for their DNA-binding, genoprotective or genotoxic potential, including their metabolites. We hope that future preclinical research (*in vitro* and *in vivo*) and

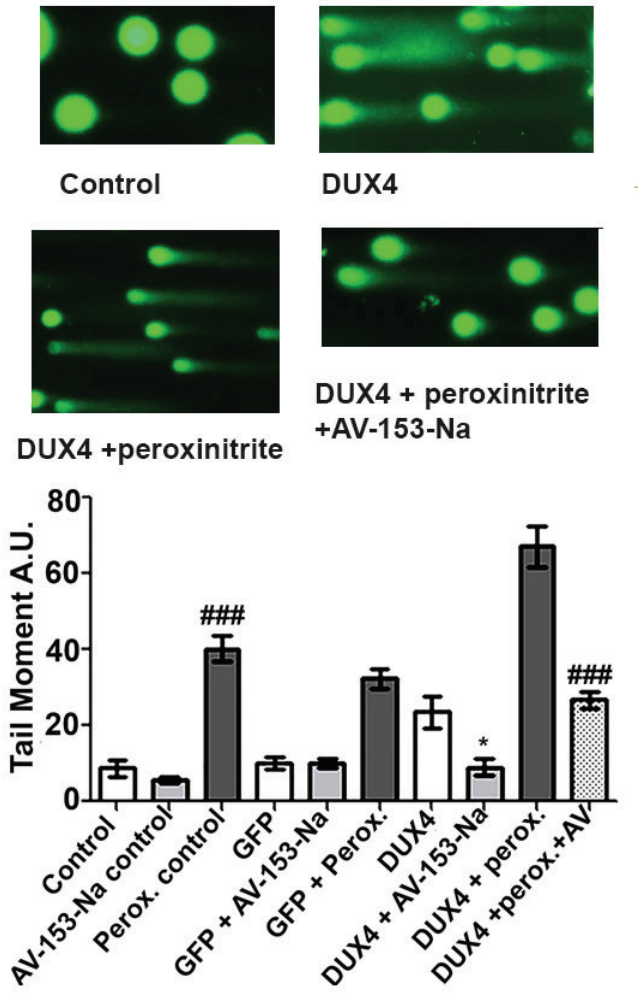

Figure 3 Protective effects of AV-153-Na (50 nmol/L) against DNA oxidative damage caused by the DUX4 protein in the HeLa cell line. *p<0.05 vs DUX4. ###p<0.001 vs DUX4 + peroxynitrite. A.U. – arbitrary units; GFP – transfection control

pharmacokinetic studies in particular, will be able to pinpoint the exact mechanism(s) of their genotoxic and/or genoprotective action.

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Kratki pregled genotoksičnoga i genoprotektivnoga djelovanja derivata 1,4-dihidropiridina

Ovaj pregledni rad donosi sažetak onoga što smo dosad naučili o genotoksičnom i genoprotektivnom djelovanju 1,4-dihidropiridina (DHP), s posebnom pažnjom na 1,4-DHP-ove topljive u vodi. Većina tih u vodi topljivih spojeva slabo aktivira blokiranje kalcijevih kanala, što se smatra "neuobičajenim" za 1,4-DHP-ove. Glutapiron, diludin i AV-153 ublažavaju spontanu mutagenezu i učestalost mutacija prouzročene kemijskim mutagenima. AV-153, glutapiron i karbatoni štite DNA od oštećenja prouzročenih vodikovim peroksidom, zračenjem i peroksinitritom. Sposobnost tih molekula da se vežu za DNA vjerojatno nije jedini mehanizam njegove zaštite, budući da su mogući i drugi mehanizmi, poput uklanjanja radikala ili vezanja za druge genotoksične spojeve koji pospješuju popravak DNA. Zbog tih nepoznanica i izvještaja da visoke koncentracije 1,4-DHP-ova oštećuju DNA, potrebno je napraviti daljnja neklinička istraživanja *in vitro* i *in vivo*, napose ona farmakokinetička, budući da mogu pomoći razaznati točne mehanizme genotoksičnoga i/ili genoprotektivnoga djelovanja derivata 1,4-dihidropiridina.

KLJUČNE RIJEČI: 1,4-DHP; AV-153; diludin; glutapiron; karbatoni; vezanje za DNA