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The Neurotropic, Anti-Inflammatory, and Antitumor Properties of the Hopantenic Acid Molecule Based on Chemoinformatic Analysis

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Hopantenic acid is a known nootropic agent with a chemical structure close to that of pantothenic acid (vitamin B5). The neurotropic effect of hopantenic acid may occur as a result of binding with δ and ϰ opioid receptors, modulating acetylcholine secretion, and interacting with dopamine receptors. Apart from the neurotropic effects, hopantenic acid can modulate the metabolism of prostaglandins and steroids, and may have antitumor actions.

Keywords: hopantenic acid, chemoinformatics, Pantocalcin.

Hopantenic acid is known as a nootropic agent. In terms of its chemical structure, hopantenic acid is a homolog of pantothenic acid (it differs by one CH_2 group), containing a γ-aminobutyric acid (GABA) residue. These structural characteristics are shown in Fig. 1.

Hopantenic acid is known to have neurometabolic, neuroprotective, and neurotrophic properties, increasing the resistance of the brain to hypoxia, and combines this with a moderate sedative effect. Hopantenic acid also has neuroleptic, anticonvulsive, nootropic, and analgesic actions [1]. In treatment, hopantenic acid (in the form of calcium hopantenate (Pantocalcin)) is used in cerebrovascular pathology, hyperkinetic disorders, tremor, and as a supplementary substance in the treatment of epilepsy. Pantocalcin increases the duration of action of barbiturates and increases the efficacy of anticonvulsants, nootropes, and CNS-stimulating substances. The actions of hopantenic acid are enhanced by combination with glycine [2].

Despite a quite wide spectrum of neurotropic effects, the precise mechanisms of action of hopantenic acid and its salts remain to be determined. It has been suggested that all the effects of hopantenic acid are mediated exclusively by interaction with GABA receptors. We present here the results of our analysis of the potential molecular mechanisms of the action of hopantenic acid, established by state-of-the-art information technology-based chemoinformatic analysis [3, 4].

Methods

Chemoinformatics is an area of studies in molecular pharmacology [5] at the junction of structural chemistry and informatics in which interactions of the "chemical structure" – "property" type are studied by contemporary informatics methods. Chemoinformatic analysis of hopantenic acid in the present work was performed by developing a novel mathematical method, based on combinatorial solvability theory [6–9].

Combinatorial solvability theory, a development of the algebraic approach to recognition tasks, was developed by the scientific school of Academician of the Russian Academy of Sciences Yu. I. Zhuravlev [10–12] and is a contemporary tool for studies of the attributional description of objects. In the case of the task of identifying molecules whose chemical structures are similar with that of a specified molecule, the study objects are *chemographs*. A chemograph (χ-graph) is a particular type of graph (i.e., a mathematical object representing a set of multiple vertexes and edges – the latter being

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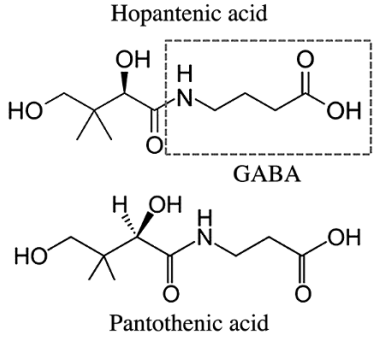

Fig. 1. Chemical structure of hopantenic acid.

the links between the vertexes). A chemograph is a finite connected nonoriented mapped graph without loops, with a clique number not greater than 3.

In combinatorial solvability theory, χ-graphs are regarded as objects and their invariants (or cortege of invariants) as an attributional description of the objects. As applied to chemographs, the completeness theorem of the invariant cortege of a selected chemograph and the correspondence of the completeness criterion of the invariant to the solvability/regularity criterion are important, and the main result can be described as:

$$\underset{a,b\in Pr}{\forall} iso(a)\neq iso(b)\Rightarrow \underset{i=1..|\chi|}{\exists} i:\hat{\imath}[i]\chi(a)\neq\hat{\imath}[i]\chi(b), \quad (1)$$

where Pr represents the multiple precedents of the graphs (obtained from the specified set of molecular structures), *iso*(G) is a label indicating that graph G belongs to some class of isomorphic graphs (evident from the descriptions of molecules in the chemical structures database), **χ** is a multiplicity of elementary χ-invariants (fragments of chemical structures), iχ is the cortege invariant (list of fragments of structures used in the structure of any molecule). If condition (1) is fulfilled for the set **χ** of interest, then **χ** ensures solvability of the task over Pr and allows systematic studies of all the fragments of the carbon skeletons of organic molecules. If set Pr is regular, i.e., does not contain two identical chemographs (molecules), then set **χ** is established on the basis of the standard approach to calculation of the characteristic function of the set of informative values of characteristics T(α) [6, 8] for set **χ**, as T(α) and $\alpha\in\chi$ are determined on the basis of selection of the element of the cortege invariant (i.e., the type of carbon skeleton fragment) with the greatest informativeness ranking α:

$$T(\alpha)=\begin{cases}1 \text{ if } \underset{a,b\in Pr}{\exists}:(\hat{\imath}[\alpha]\chi(a)\neq\hat{\imath}[\alpha]\chi(b))\wedge \\ \quad \wedge(\forall k<\alpha\Rightarrow\hat{\imath}[k]\chi(a)=\hat{\imath}[k]\chi(b)), \quad (2)\\ 0 \text{ otherwise.}\end{cases}$$

This procedure yields that cortege invariant which would allow each chemograph (molecule) in Pr to be distinguished from all others. Tests (1, 2) were performed on random selections of 50000 pairs of molecules with different structures from the PubChem database [13] using binary cortege invariants over a set of χ-chains (chain fragments of chemical structures) of length *n* (*n* = 1–7). These calculations showed that at *n* = 7, the accuracy of discrimination of one molecule from another was 99.4% and quite high accuracies (93–97%) were obtained with even shorter χ-chains (*n* = 4, 5).

The resulting set **χ** and the *Hamming metric* were used to determine the function of the distance between chemographs d_χ over binary χ-invariants as follows:

$$d_\chi(X_1,X_2)=\frac{1}{|\chi|}\sum_{i=1}^{|\chi|}\hat{\imath}[i]\hat{\beta}[X_1]\chi\oplus\hat{\imath}[i]\hat{\beta}[X_2]\chi. \quad (3)$$

This expression, reflecting the "chemical distance" between two selected molecular structures, was also used to generate a list of molecules with structural similarity to hopantenic acid.

Thus, at the first stage of the chemoinformatic analysis, the distance dχ was used to establish a list of chemical structures most similar to hopantenic acid. Then, for each molecule in this list, all existing experimental measurements of the various biological properties of the molecule were extracted from the database. For each of these properties, where values of the corresponding constants needed to be calculated (binding constant, inhibition constant, etc.), all similar molecules for which this property had been measured were selected and an empirical function of the distribution of the values of these constants was constructed.

The values for the values of constants presented henceforth were obtained as the mathematical expectation and variance of the corresponding empirical distribution functions, which were used after the corresponding filtration with i-spectra to form a continuous ubiquitous differentiation function and analysis of modality (i.e., number of peaks).

Results and Discussion

During the analysis, the chemical structure of hopantenic acid was compared with those of three databases of small molecules: the PubChem database of all known small molecules [13], the Human Metabolome Database (HMDB) [14], and the Protein Data Bank (PDB) [15]. Analysis of results from these three collections of molecules pointed to the following possible effects of hopantenic acid: neuroprotective activity, metabolism of prostaglandins and regulation of inflammation, regulation of steroid metabolism, and antitumor properties.

The PubChem database contains the structures of about 100 million molecules along with results of measurements of the various biological properties of these molecules (receptor affinities, different types of biological activ-

TABLE 1. Structural Similarities between Hopantenic Acid and Molecules with Neurotropic Activity

dχ	Molecule	Receptor protein	Presumptive clinical effect
0.19	Inhibitor BMS948	RARβ retinoids receptor	Improvement in color vision
0.25	Acetylamino-2-oxo-2-3-indolylacetamide	MT3 melatonin receptor	Maintenance of sleep-waking rhythm
0.31	3,4-Dihydroisoquinolinone	Phosphoinositide-dependent kinase 1 (PDK1)	Maintenance of effects of myoinositol (vitamin B8)
0.32	3-Methylpiperidyl quinoxalylmethanone	Glutamate receptor 2 (GLUA2)	Neuroprotection, decreased excitoxicity
0.32	Rolipram	Phosphodiesterase-4	Nootropic and neuroprotective effects
0.33	L-Theanine	Under study	Nootropic effect
0.33	6-Chloro-1,3-dihydroindolone	Phenylethanolamine N-methyltransferase	Regulation of adrenaline biosynthesis, balance of sympathetic/parasympathetic systems
0.36	2-Pyrrolidinone	Under study	Neuroleptic and nootropic effects
0.39	4-Acetamidobutanoate	Under study	GABA derivative
0.39	Pyroglutamate	More than 10 proteins	Neuroprotective and neurotrophic properties

TABLE 2. Assessment of Neurotropic Properties of Hopantenic Acid

dχ	*n*	*M*	*m*	Test	Units	Function
0.09	3	1948	420	IC_{50}	nM	Cannabinoid GPR55 receptor antagonist
0.13	5	15	11	—	%	Increases acetylcholine secretion in rat striatum
0.13	5	620	1190	EC_{50}	nM	Stimulation of dopaminergic receptors
0.13	18	2807	2642	IC_{50}	nM	Inhibition of human glycine transporter
0.17	2	75	11	E_{max}	%	Agonist of human δ opioid receptors
0.17	2	23	8	EC_{50}	nM	Agonist of δ opioid activity in human cells
0.17	2	105	52	E_{max}	%	Agonist of human ϰ opioid receptors
0.17	2	17	9	EC_{50}	nM	Agonist of human ϰ opioid receptors
0.17	2	39	8	E_{max}	%	Agonist of human μ opioid receptors
0.17	2	100	50	EC_{50}	nM	Agonist of human μ opioid receptors
0.17	2	65	33	I_{max}	%	Antagonist of μ opioid receptor
0.17	2	34	29	IC_{50}	nM	Antagonist of μ opioid receptor
0.17	4	149	130	–	–	Selectivity of ϰ opioid/μ opioid receptors
0.17	4	101	52	–	–	Selectivity of δ opioid/μ opioid receptors

Notes. *n* is the number of similar molecules used for calculation of the constant; dχ is the maximum distance from the similar molecules to the hopantenic acid molecule; *M* is the mean error of the constant; *m* is the standard deviation of the value of the constant. The IC_{50} (the concentration producing half-maximal inhibition) shows how much inhibitory ligand is required for 50% inhibition of the biological process. E_{max} is the maximum possible effect for the agonist concerned (% of the activity of a standard agonist of the protein receptors). EC_{50} is the concentration at which an effect of $0.5E_{max}$ is obtained.

ity, etc.). This dataset was used to calculate the biological activity constant.

The HMDB database contains the structures of more than 35000 molecules in the human metabolome and a number of drugs. The PDB database is a set of 19000 small molecules with different protein structures. Comparison of the chemical structure of hopantenic acid with molecules in the HMDB and PDB databases provided important additional information of the biological properties of Pantocalcin.

The main proposed properties of hopantenic acid, identified on the basis of chemoinformatic analysis, were then examined sequentially: neurotropic activity, effects on prostaglandin metabolism, modulation of steroid metabolism, and antitumor properties.

Molecular mechanisms of the neurotropic activity of hopantenic acid. Previous scientific and clinical studies have demonstrated the cerebroprotective action of hopantenic acid [16]. For example, investigations reported in [17] on the efficacy of Pantocalcin in the post-operative cognitive correction of dysfunctions in schoolchildren undergoing surgery under general anesthesia showed that hopantenic acid (40 mg/kg for one month after surgery) significantly

TABLE 3. Physiological Roles of Opioid Receptors

Receptor	Tissue	Function
μ	Brain (cortex, thalamus, spinal cord, substantia gelatinosa, gastrointestinal tract)	Analgesia, elevated mood, chemical dependence, suppression of respiration, pupillary contraction, weakening of gastrointestinal tract peristalsis
δ*	Brain (pontine nucleus, amygdaloid body, thalamus, deep layers of the cortex)	Analgesia, antidepressant effect, decreased chemical dependence
ϰ*	Brain (hypothalamus, gray matter, spinal cord, substantia gelatinosa)	Analgesia, sedative effect, pupillary contraction, suppression of vasopressin release (antidiuretic hormone, increases reabsorption of water by the kidneys)

* Types of receptors mainly activated on interaction by hopantenic acid.

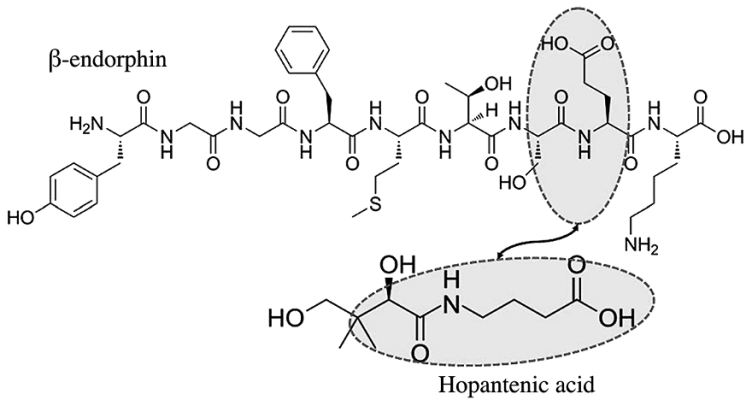

Fig. 2. Similarity of the chemical structure of hopantenic acid and β-endorphin.

decreased the severity of post-operative cognitive dysfunction [17].

Analysis of the similarity of the structure of the hopantenic acid molecule with millions of molecules in the PubChem database showed that hopantenic acid can show neurotropic effects, stimulating acetylcholine secretion (on average by 15%), binding to cannabinoid GPR55 receptors (which are activated by the endocannabinoids anandamide, 2-arachidonoylglycerol, and noladine), dopamine receptors, opioid receptors, and the glycine transporter (Table 1).

We note that chemoinformatic analysis indicated that hopantenic acid has quite high affinity for GABA receptors: EC_{50} was about 12000 ± 5000 nm for different GABA receptor types. We note that the EC_{50} (the half-maximal effective concentration) is the concentration of ligand at which an effect half of the maximum possible develops. Higher EC_{50} values therefore correspond to lower levels of affinity of ligand for receptor. At the same time, measured EC_{50} values for opioid and dopamine receptors were several orders of magnitude lower than the EC_{50} of hopantenic acid for GABA receptors (Table 2).

These data were used to assess the affinity of hopantenic acid for different types of opioid receptor. Among the effects demonstrated, there is particular interest in the modulation of opioid receptors, as the corresponding EC_{50} and IC_{50} values differed, on average, by an order of magnitude as compared with other receptor types (see Table 1).

Opioid (opiate) receptors are G-protein-coupled receptors in the CNS, widely distributed in the brain and spinal cord, the gastrointestinal tract, and other organs [18]. Activation of opioid receptors regulates ion channels: closure of voltage-gated Ca channels in presynaptic neurons leads to decreased release of excitatory neurotransmitters (glutamate), while activation of K channels on postsynaptic neurons leads to membrane hyperpolarization and a decrease in the sensitivity of neurons to excitatory neurotransmitters [19]. Modulation of opioid receptors is an important trend in the pharmacology of substances decreasing chemical dependence.

Four main groups of opioid receptors are currently recognized: μ (mu), δ (delta), ϰ (kappa), and nociceptive receptors [20]. Analgesic effects are seen on stimulation of μ, δ, and ϰ receptors. μ receptor agonists also suppress respiration and produce a sedative effect, while ϰ receptor agonists also have psychotomimetic effects [21]. The physiological role of these varieties of opioid receptors are summarized in Table 3.

Chemoinformatic analysis showed (see Table 2) that hopantenic acid can interact with δ, ϰ, and μ opioid receptors. Hopantenic acid is probably an agonist of δ and ϰ receptors, stimulating receptor activity by up to 75–100%. At the same time, hopantenic acid is most likely an antagonist

TABLE 4. Assessment of the Properties of Hopantenic Acid as a Regulator of Prostaglandin Metabolism

dχ	*n*	*M*	*m*	Test	Units	Function
0.09	14	3200	350	IC_{50}	nM	Affinity for rat prostaglandin E2 receptors (EP2)
0.09	14	815	925	IC_{50}	nM	Affinity for rat EP4 receptor
0.09	9	164	156	EC_{50}	nM	Activity on rat EP4 (camp accumulation)
0.09	9	98	9	EC_{50}	%	Activity on rat EP4 (camp accumulation)
0.09	3	1785	2345	K_i	nM	Affinity for human EP2 receptors
0.09	3	1672	699	K_i	nM	Affinity for human EP3 receptors
0.09	3	391	508	K_i	nM	Affinity for human EP4 receptors
0.09	3	93	67	EC_{50}	nM	Functional activity of human EP4 receptor

Notes. *n* is the number of similar molecules used for calculation of the constant; dχ is the maximum "distance" from the similar molecules to the hopantenic acid molecule; *M* is the mean error of the constant; *m* is the standard deviation of the value of the constant.

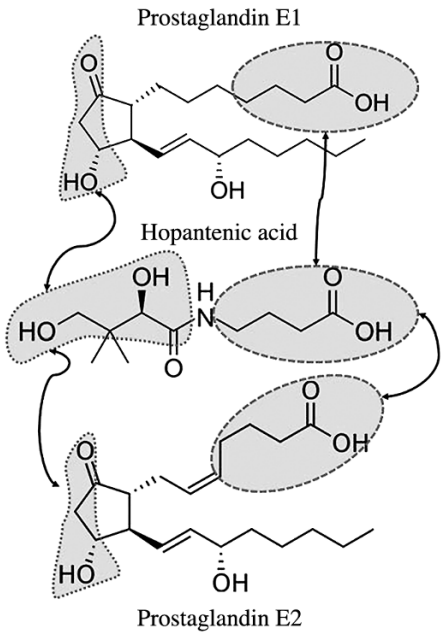

Fig. 3. Similarity of the chemical structure of prostaglandins E and hopantenic acid.

of μ opioid receptors (as an agonist: +39% activity; as antagonist: –65% of activity; see Table 2). Analysis of selectivity showed that hopantenic acid is 100 times more selective for κ and δ opioid receptors than for μ receptors.

Among the opioid neurotransmitters, endorphins and endomorphines have maximal affinity for μ receptors, enkephalins for δ receptors, and dynorphins for κ receptors [22]. Chemoinformatic analysis results therefore suggest that in terms of its effects, hopantenic acid may be closer to enkephalins and dynorphins than to endorphins. Endorphins (endogenous morphines activate mainly μ receptors) are peptide neurotransmitters with the ability to decrease pain and affect emotional state. They are formed from β-lipotrophin and control the activity of the endocrine glands. The chemical structure of β-endorphins shows elements of similarity with that of hopantenic acid (Fig. 2).

As regards enkephalins, these mainly activate δ receptors and, along with other opioids, take part in regulating behavior and feelings of pain. Leu-enkephalin and met-enkephalin are distinguished. Met-enkephalin is a hormone from the intermediate lobe of the hypophysis (γ-melanocyte-stimulating hormone is synthesized and secreted along with met-enkephalin).

Activation of δ receptors has an analgesic effect; at high doses, agonists can induce convulsions [23]. Agonists of δ receptors can stimulate respiratory function and block the suppressive influences of μ opioid receptor agonists such as altenafil on respiratory function [24]. Activation of δ receptors also has an antidepressant effect and increases the brain-derived neurotrophic factor (BDNF) level. Agonists of δ opioid receptors have a cardioprotective effect, decreasing myocardial tissue damage in transient ischemia [25, 26]. As hopantenic acid can activate δ opioid receptors, Pantocalcin has the positive pharmacological effects listed above to some extent or other.

Hopantenic acid can also activate κ opioid receptors. Physiological activation of κ receptors occurs mainly as a result of dynorphins – endogenous opioid peptides with analgesic activity. There are elements of similarly between the hopantenic acid molecule and dynorphins. Activation of κ receptors is believed to counter the effects of activation of μ receptors [27]. Activation of κ receptors produces a diuretic action (via a decrease in the vasopressin level) [28] and has a neuroprotective effect in cerebral ischemia [29].

Analysis of the similarity between hopantenic acid molecules and the protein structures of known ligands points to a high level of similarity between the chemical structures of hopantenic acid and various neurotropic substances (these data are presented in Table 1). We note that the distance dχ between pantothenic acid and such B5 vita-

Fig. 4. Finger clubbing (ICD-10 R68.3), which is associated with increased EP2 prostaglandin receptor activity.

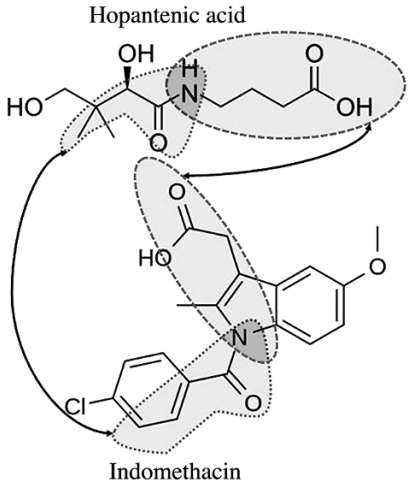

Fig. 5. Elements of structural similarity of hopantenic acid and indomethacin.

mers as pantothenamide, pantein, and pantothenic acid, was $d\chi = 0.40–0.42$, while the distance from the molecules listed in Table 1 was $d\chi = 0.19$

Chemoinformatic analysis suggested additional mechanisms for the neurotropic and nootropic actions of hopantenic acid, such as modulation of retinoid metabolism (binding with retinoid RARβ receptors), maintenance of the various positive effects of myoinositol (vitamin B8) [30–32], binding with melatonin MT3 receptors, inhibition of the glutamate type 2 receptor (GLUA-2), and selective inhibition of phosphodiesterase-4 (which improves long-term memory and has a neuroprotective effect). In addition, it shows similarity with theanine (which has caffeine-like psychoactive and nootropic properties), 2-pyrrolidone (whose derivatives include such nootropic pharmaceuticals as doxapram and piracetam), and pyroglutamate, which has numerous neuroprotective and neurotropic properties [5].

Prostaglandin metabolism and the regulation of inflammation. Analysis of the similarity of the structure of hopantenic acid with molecules in the PubChem database showed that hopantenic acid may have a significant action on prostaglandin metabolism due to binding with EP2 and EP4 prostaglandin receptors and stimulation of the corresponding biological activities (Table 4). The main elements of similarity between the chemical structures of group E prostaglandins and hopantenic acid are shown in Fig. 3.

Chemoinformatic analysis data (see Table 4) indicated that hopantenic acid can inhibit prostaglandin E2 receptors (EP2 receptors) and activate eicosanoid receptors for prostaglandins E (E4 receptors). This profile of interactions with prostaglandin metabolism is consistent with an anti-inflammatory effect.

EP2 receptors specifically bind prostaglandin E2, whose biological activity is associated with allergic reactions and aspirin-induced asthma. It is widely recognized that prostaglandin E2 stimulates an increase in temperature (hyperthermia). In addition, increased EP2 receptor activity is associated with congenital heart defects and, presumptively, with the symptom of nail clubbing [33].

Nail clubbing (ICD-10, R68.3) consists of bulb-shaped thickening of the terminal phalanges of the fingers and toes in chronic diseases of the heart and lungs, with a characteristic deformation of the nail plate (Fig. 4). The tissue between the nail and the underlying bone becomes spongiform, such that squeezing the base of the nail produces the feeling that the nail plate is mobile. Thickening of the distal phalanges of the fingers and toes occurs as a result of growth of the connective tissue between the nail plate and the bone. "Club fingers" constitute an informative sign of diseases and pathological processes.

Chemoinformatic analysis results indicate that hopantenic acid has much greater affinity for EP4 prostaglandin receptors than other receptor types. In fact, the calculated values for the binding constant are 3–10 times lower for EP4 than for EP2 (see Table 2). In other words, hopantenic acid affects EP4 receptors at much lower concentrations than EP2 and P3 receptors.

EP4 prostaglandin receptors are involved in transmitting T-cell activation signals, initiating the cutaneous immune response, and regulating the cyclooxygenase-2 mRNA level. Activation of EP4 also has positive effects in myocardial ischemia, decreasing the size of the ischemic zone as a result of activation of the cAMP and myoinositol-dependent PI3K kinase signal pathways. The cardioprotective action of activated EP4 receptors is also linked with decreases in inflammatory processes in the ischemia zone [34]. Thus, hopantenic acid can show an anti-inflammatory effect via inhibition of EP2 receptors and activation of EP4 receptors.

Analysis of small molecules in the PDB protein complexes database showed that hopantenic acid can bind not only with prostaglandin receptors, but also with other proteins involved in prostaglandin metabolism: phospholipase A2, cyclooxygenase-2, prostaglandin-H2 synthase, and leukotriene A4 hydrolase (Table 5). In particular, there is struc-

TABLE 5. Structural Similarity of the Hopantenic Acid Molecule and Proteins Involved in Prostaglandin Metabolism and the Regulation of Inflammation

dχ	Molecule	Receptor protein
0.25	6,7-Diphenylheptanoyl aminohexanoate	Human phospholipase A2 with substrate analog
0.29	Indomethacin	Cyclooxygenase-2 with indomethacin inhibitor
0.29	Iodoindomethacin	Prostaglandin H2 synthase-1 with iodoindomethacin
0.29	2'-Desmethylindomethacin	17β-Hydroxysteroid dehydrogenase 5 (AKR1C3)
0.32	2-Amino-5-O-phenylmethoxyphenylpentanoate	Leukotriene A4 hydrolase
0.33	6-Bromodihydroindolone	Human chymase
0.33	2-Hydroxy-N-phenylbenzamide	Cardiac mitochondrial complex II
0.33	4-CN-2-phenylcyclopropyl benzamide	Human epoxide hydrolase with inhibitor
0.33	6,8-Disulfanoyloctanoyl-lysine	Mitochondrial matrix protein histidine kinase PDHK2-L2
0.35	4-Methoxytrifluoromethyl benzoylpentanoate	Ligand-binding domain of PPARγ (peroxysome proliferation activator)

TABLE 6. Hopantenic Acid and the Autitumor Modulation of Steroid Hormone Metabolism

dχ	*n*	*M*	*m*	Test	Units	Function
0.13	3	132	151	IC_{50}	nM	Inhibition of human ERα estrogen receptors
0.13	3	585	705	IC_{50}	nM	Inhibition of human ERβ estrogen receptors
0.13	2	234	226	IC_{50}	nM	Inhibition of prostate steroid 5α-reductase
0.13	4	1298	1334	IC_{50}	nM	Antagonist of rat prostate androgen receptors
0.13	5	85	21	IC_{50}	%	Inhibition of 5α-reductase
0.14	4	494	146	IC_{50}	nM	Inhibition of 17 β-hydroxysteroid dehydrogenase
0.14	5	4890	3517	IC_{50}	nM	Inhibitor of RORγ receptors
0.14	3	5477	4837	IC_{50}	nM	Inhibition of human 5α-reductase
0.14	4	2950	1016	IC_{50}	nM	Inhibition of rat liver microsomal acyl-coenzyme A:cholesterol acyltransferase 1

tural similarity between hopantenic acid and the non-steroidal anti-inflammatory substance indomethacin (Fig. 5).

Regulation of steroid metabolism and antitumor effects. Apart from the neurotropic and anti-inflammatory effects described above, chemoinformatic analysis demonstrated the possibility that hopantenic acid has antitumor actions (Tables 6–8). In particular, the potential antitumor activity of hopantenic acid may be mediated by modulation of steroid metabolism.

Chemoinformatic evaluation of the binding constant showed that hopantenic acid would be expected to have antitumor effects at quite moderate doses, of 100–5000 nM, which corresponds to around 20–1000 μg/kg. Taking account of the quite long half-elimination period of hopantenic acid (10–12 h) [35], the assessed effective dose is 12 to 300 mg/kg.

The potential effects of the action of hopantenic acid on steroid metabolism are linked with inhibition of human ERα and ERβ estrogen receptors (mainly ERα), antagonism of androgen receptors, and, overall, inhibition of steroid metabolism (see Table 6). In particular, hopantenic acid can inhibit steroid 5α-reductase in the prostate – an enzyme involved in androgen and estrogen biosynthesis, inhibition of which is used in benign hyperplasia of the prostate, male baldness, and other impairments linked with excess testosterone. Hopantenic acid can produce partial inhibition of 17β-hydroxysteroid dehydrogenase, which converts androstenedione and testosterone, estrone, and estradiol in the presence of cofactor NAD^+ (vitamin PP).

The antiproliferative activity of hopantenic acid may also be mediated by activation of the cytochrome system, modulation of melanocyte-stimulating receptor receptors (see Table 7), and increases in the stability of genomic DNA (see Table 8).

Hopantenic acid can produce moderate activation of CYP2C9 and CYP1A2 (the activation constant AC_{50} was ~5 μM; compounds with constants of less than 10 μM are generally regarded as active). The enzyme cytochrome P450 is known to detoxify many cancerogenic substances. For example, cytochrome CYP2C9 metabolizes more than 100 drugs, including warfarin, phenytoin, acenocoumarol, tolbutamide, losartan, glipizide, and various nonsteroidal

TABLE 7. Possible Antitumor Properties of Hopantenic Acid

dχ	*n*	*M*	*m*	Test	Units	Function	Presumptive clinical effect
0.09	14	1354	1428	IC50	nM	Antiproliferative effect (MDA468 cells)	Decrease in rate of development of malignancy of breast cancer cells
0.13	6	8615	8756	AC50	nM	Activation of CYP2C9	Detoxification of cancerogenic substances
0.13	6	7305	6959	AC50	nM	Activation of CYP1A2	
0.17	9	3789	4221	IC50	nM	Antagonist of human TRPV1 receptors	Regulation of inflammatory response of intestinal epithelium
0.17	6	4050	1947	Ki	nM	Affinity for human MC1 receptors	Melanogenesis, DNA repair, anti-inflammatory and antioxidant effects, decreased risk of skin and retinal melanoma
0.17	6	4050	1335	Ki	nM	Affinity for human MC4 receptors	
0.17	6	5733	4736	Ki	nM	Affinity for human MC5 receptors	

TABLE 8. Similarity between the Hopantenic Acid Molecule and Receptor Proteins Involved in Maintaining DNA Structure and Genome Stability

dχ	Molecule	Receptor protein	Presumptive effect
0.25	Phenylcarbonylaminophenylpropionate	LSD1-CoREST lysine-specific demethylase-1	Genome stability
0.25	Cyclopropyl-cyclopropylmethyl-6-methylbiphenyl-3,4-dicarboxamide	p38 kinase complexed with inhibitor	Antioxidant and anti-inflammatory effects
0.25	3,4-Dihydro-5-methylisoquinoline	Poly(ADP-ribose) polymerase	Repair of DNA damage
0.25	Butanoyl-lysine	Histone H3-K protein Brd4 associates with chromosomes during cell division	Repair of DNA damage
0.29	4-Methyl-benzoylamino-biphenyldicarbonohydroxyamide	HDAC8 histone deacetylase	
0.31	Phenanthridinone	Poly(ADP-ribose) [olymerase 14 (PARP14/ARTD8)	Maintenance of genome stability
0.31	Tetradecanoyl-L-lysine	SIRT6 stress response protein	
0.35	2-Aminoethylcarbamoyl-2,2'-bipyridinecarbonate	JMJD2A Lysine-specific demethylase 4A	

anti-inflammatories. Cytochrome CYP1A2 inactivate polyaromatic cyclic hydrocarbons in cigarette smoke, aflatoxin B1, and acetaminophen.

Chemoinformatic analysis indicated that hopantenic acid has moderate affinity for melanocyte-stimulating hormone MC1, MC4, and MC5 receptors (inhibition constants K_i of the order 4000–6000 nM). Melanocyte-stimulating hormones (MSH) – melanotropins, melanocortins – are secreted by the intermediate lobe of the hypophysis and their main function is melanogenesis in melanocyte cells in the skin and hair, and also in the pigmented layer of the retina. Increased MSH activity leads to darkening of the skin(for example in pregnancy).

Apart from activation of melanocytes, MSH also has other functions in the human body: it increases DNA repair after damage by UV light [36], inhibits activation of the proinflammatory factor NF-κB [37], and suppresses oxidative stress [38]. The MC4 receptor is involved in regulating feeding behavior and metabolism, while defects in the *MC4R* gene are associated with inherited excessive body weight. Experimental deletion of the MC5R gene leads to impairments in the operation of the external secretory glands [39, 40]. All these effects of MSH receptors may contribute to the antiproliferative activity of hopantenic acid.

Analysis of molecules in the PDB protein structures database indicated possible additional mechanisms for the antitumor activity of hopantenic acid (Table 8). Lysine-specific demethylase LSD1-CoREST supports the optimum level of folate-dependent DNA methylation, poly-(ADP-ribose)-polymerase maintains DNA damage repair processes and chromatin remodeling, and proteins Brd4, SIRT6, histone deacetylase HDAC8, and lysine-specific 4A JMJD2A demethylase are important for maintaining the structures of histone proteins, which maintain the compact packaging of DNA molecules in the cell nucleus, increasing the stability of genomic DNA. Greater genome stability corresponds to greater antitumor immunity regardless of the particular type of tumor.

The data presented here lead to the conclusion that hopantenic acid and its salts (for example, calcium hopantenate, the active ingredient of Pantocalcin) have nootropic actions.

This effect is believed to result mainly from the similarity of the structure of a fragment of the hopantenic acid molecule with the neurotransmitter GABA. The chemoinformatic analysis reported here suggests that the neurotropic effects of the hopantenic acid molecule may be mediated by binding with and partial activation of δ and ϰ receptors, modulation of acetylcholine secretion, and interaction with dopamine receptors.

In addition, chemoinformatic analysis results for hopantenic acid point to potential anti-inflammatory (modulation of prostaglandin metabolism) and antitumor effects (modulation of steroid metabolism, increased stability of genomic DNA). We note that achievement of anti-inflammatory effects in neurology sometimes requires special anti-inflammatory agents. The fact that a neuroprotector prescribed as long courses has anti-inflammatory effects is a clear advantage of the agent concerned. Chemoinformatic analysis results point to great potential for further basic and clinical studies of Pantocalcin.

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