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REVIEW ARTICLE

Antiepileptogenic Effect of Retinoic Acid

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Abstract: Retinoic acid, a metabolite of vitamin A, acts through either genomic or nongenomic actions. The genomic action of retinoids exerts effects on gene transcription through interaction with retinoid receptors such as retinoic acid receptors (RARα, β, and γ) and retinoid X receptors (RXRα, β, and γ) that are primarily concentrated in the amygdala, pre-frontal cortex, and hippocampal areas in the brain. In response to retinoid binding, RAR/RXR heterodimers undergo major conformational changes and orchestrate the transcription of specific gene networks. Previous experimental studies have reported that retinoic acid exerts an antiepileptogenic effect through diverse mechanisms, including the modulation of gap junctions, neurotransmitters, long-term potentiation, calcium channels and some genes. To our knowledge, there are no previous or current clinical trials evaluating the use of retinoic acid for seizure control.

Keywords: Epilepsy, seizures, antiepileptic, retinoic acid, genes, retinoids.

1. INTRODUCTION

One of the most prevalent neurological disorders is epilepsy, distinguished by periodic and uncertain seizures [1]. Despite being such a common disorder, its underlying mechanisms are not completely studied. Antiepileptic drugs are still being developed, however about one-third of the population with epilepsy become medically refractory. Overall, these drugs cannot fully control seizures or have unbearable side effects [2]. In consequence, effective antiepileptic alternatives must be researched. In this matter, the role of retinoic acid in epilepsy presents itself as an opportunity to further understand the pathophysiological aspects of epilepsy, as well as to allow the finding of a new possible treatment. This review intends to describe the biology, biosynthesis and signaling of retinoids; and explore the evidence about the antiepileptogenic effect of retinoic acid. Finally, it presents the main reports of genes involved in downregulation and upregulation of neuronal excitability regarding retinoid acid administration and the evidence of retinoid related genes in epilepsy.

2. BIOLOGY OF RETINOIDS

All over the body, retinoids carry out significant functions. Retinoic acid determines the proliferation and differentiation of cells, plays an important role in eyesight, through apoptosis it causes cell death, plays a key role in osteogenesis and embryogenesis and activates genes for tumor suppression [3-6]. As it is well known, retinoids perform their mechanisms through the regulation of expression of specific genes. Natural retinoids are composed of four isoprenoid units linked together. Overall, the term retinoid comprises natural and synthetic compositions similar to vitamin A, even if there is no biological activity concerning vitamin A [7]. Thus, diverse forms of retinoids are found in the body, both natural and synthetic. These are originated by changes in the molecular terminal polar end group. The most common retinoid types are retinyl and retinol; all-trans-retinol is the one with biological activity, *i.e.*, all-trans-retinol is vitamin A. We find the emergence of retinyl ester when there is esterification of a fatty acyl group to the retinol hydroxyl terminus [8, 9]. On the other hand, synthetic retinoids are the result of medical and pharmacological research.

3. RETINOIC ACID BIOSYNTHESIS

What makes retinol accessible to all cells is its lipophilic quality combined with its general circulation. Nevertheless, there are many tissues that cannot oxidize retinol to retinoic acid. It will only happen if there is a demand for retinoic acid within the tissue. The synthesis of retinoic acid as an ability of the cell as well as the signalization of retinoid is regulated by the retinoic acid synthetic enzymes expression [10]. Retinol is first converted into retinaldehyde, a reversible reaction catalyzed by retinol dehydrogenases (RDHS) primarily RDH1 and RDH10 and dehydrogenase/reductase (SDR family) member 9 (DHRS9). Retinaldehyde is then converted into retinoic acid in an irreversible reaction catalyzed by retinaldehyde dehydrogenases (RALDH1, 2 and 3). Embry-

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ology, in both human and mouse, has shown the expression of three isoforms of RALDH within tissues [11, 12].

4. ACTION OF RETINOIDS

To execute their functions, retinoids must link themselves to specific proteins. For instance, retinoids in bodily fluids are transported through epididymal retinoic acid binding protein (ERABP) and plasma retinol-binding protein (RBP). In the same way, retinoids within cells are transported through cellular retinoic acid-binding proteins (CRABPS) and cellular retinol-binding proteins (CRBPS) [13, 14]. The action of retinoids is of two types: genomic action and non-genomic action. The first one induces or inhibits the expression of genes, the second one regulates signaling pathways that depend on specific target phosphorylation.

There are two kinds of receptors, which are part of a large nuclear hormone receptor family: retinoic acid receptors (RARs) and retinoid x receptors (RXRs), which mediate retinoic acid signaling. The process of DNA sequences binding in the responsive genes regulatory region by these receptors to further activate or repress transcriptions is called retinoic acid response elements (RARES). Specifically, all-trans-retinoic acid (at-ra) is known for binding RARs; and 9-cis-ra, a stereoisomer executes as a ligand for both receptors. To bind RARES, comprised of nuclear receptors mediating retinoic acid effects as they are DR0 [15], DR1 [16-18], DR2 [19, 20], DR5 [21], simple DR8 [15], composite DR8 [15] and IR0 [22], a heterodimer is formed from RAR and RXR (Fig. **1**) [23-25]. Additionally, RARs can also have non-genomic functions, which is the case of RARα. Among these functions, we find the protein translation regulation of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit glutamate receptor 1 (GLUR1) by cytoplasmic RARα, while RARα binds to sequences in the GLUR1 mRNA 5′utr [26]. Furthermore, it is known that retinoic acid-binding, after the interaction of RARα with mRNAs *via* its ligand-binding domain, is a disruption of the interaction and a relief of translation repression. Likewise, studies carried out suggest that through RARα, retinoic acid may control, through membrane trafficking and non- genomically, the synaptic activity by regulating GABA receptors [27]. In addition to the control of transcription in the nucleus by RARs, a cytoplasmic function of RARs becomes evident due to the control observed in translation by these receptors. Recent evidence reports additional non-nuclear functions of RARs in relation to kinase control that promotes cellular changes [28].

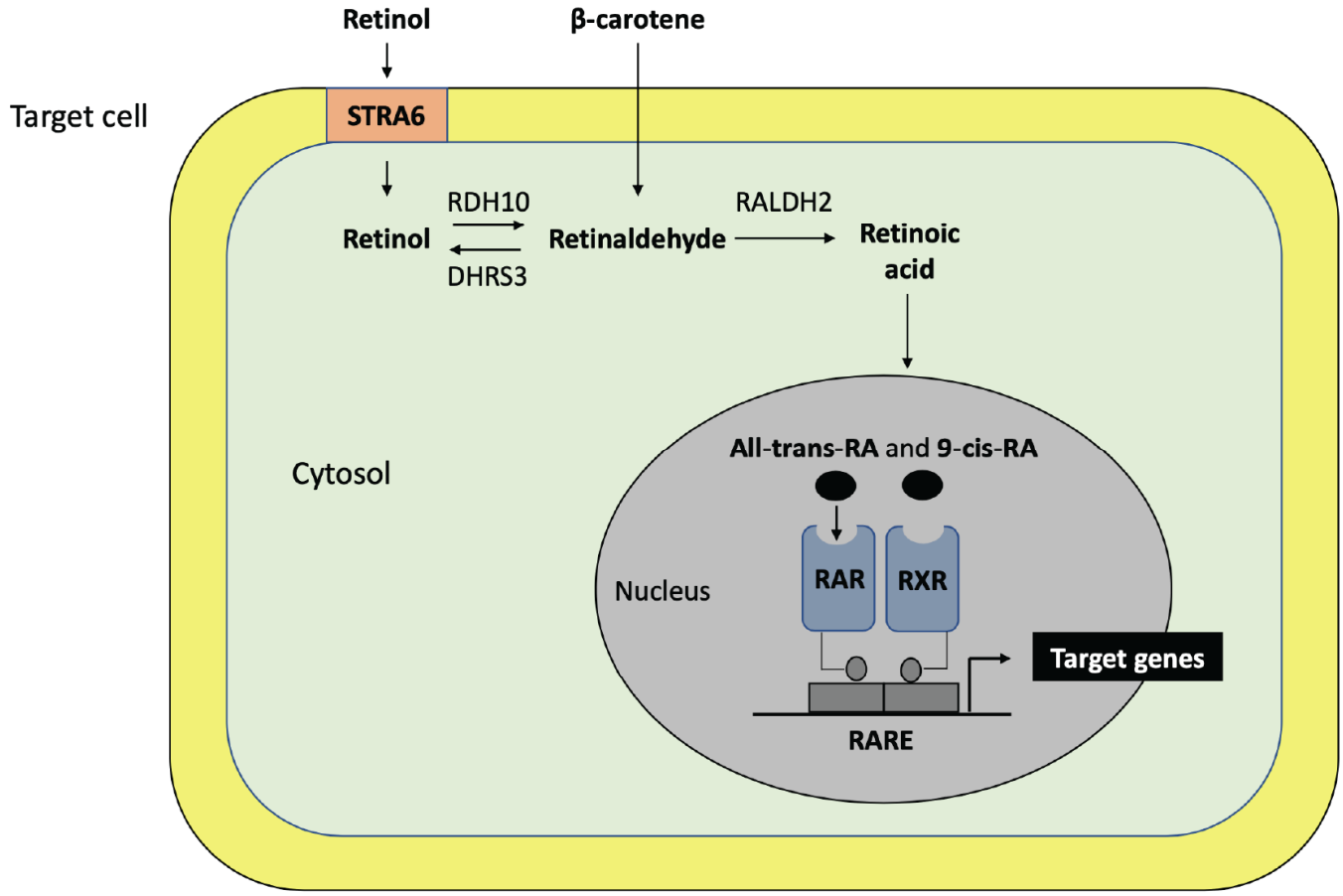

Fig. (1). Signaling of retinoids. Retinyl esters, retinol, and β-carotene are taken into the body from the diet. Both retinol and β-carotene may be converted into the transcriptionally active vitamin A forms after first being converted to retinaldehyde. Retinoic acid then regulates transcription of vitamin A responsive genes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5. ANTIEPILEPTIC EFFECTS OF RETINOIDS

5.1. Gap Junctions

Until now there is no evidence in clinical trials of the use of retinoic acid in seizures. Previous studies have demonstrated that retinoic acid in horizontal cells of the retina is an important related modulator of electrical synchronization through Gap junctions. Unlike previous reports of retinoic acid action, regulation of synaptic function does not occur through genomic mechanisms, but through its non-genomic agonist function related to external binding at the specific site with rarβ/γ-like acting as a different form of signaling second messengers [29-31]. Gap junctions are membrane channels between cells that create direct communication between the cytoplasm of two cells [32, 33]. They are formed by connexons which are hemichannels coupled from end to end, each hemichannel is made up of six connexin subunits surrounding a central pore [34-36].

It is reported both clinically and experimentally that epileptic seizures alter the expression of connexins and Gap junctions permeability [37]. *In vivo* and *in vitro* reports demonstrate Gap junctions as a therapeutic opportunity to develop targets for anticonvulsant medications. Gap junctional blockers exist but have not been used to date to treat seizures in clinical studies. Participation in the generation, synchronization and maintenance of seizures of the Gap junctions in neurons and glia cells must be evaluated in greater depth separately, for example, since Gap junctions in neurons participate predominantly in the generation of synchronous oscillations of high frequency and Gap junctions in glia cells specifically in astrocytes participate in seizure activity through two mechanisms: with the amortization of k + to regulate neuronal activity and through the supply of energy to neurons to maintain excitability [38-40]. Therefore, when the Gap junctions are open, they can promote interictal activity, increasing the amplitude of epileptic discharges and increasing the duration of seizures. On the other hand, when the Gap junctions are closed, they promote a decrease in epileptic activity and favor the cessation of epileptic seizures [41]. Retinoic acid has been reported as a gap junction blocker (Fig. **2**). It has been reported, with the kindling epilepsy model, that the administration of retinoic acid directly to the amygdala significantly reduces the amount of epileptic seizures and post-discharge that are generated electrically by stimulating the amygdala [42]. The explanation for this effect of retinoic acid in the reduction of seizures is through the inhibition of Gap junctions, as well as the increase in the expression of cx32 and cx43 [43, 44].

5.2. Electroencephalography Findings

Reports regarding experimental studies on rats and mice especially focus on the role of the dopaminergic system in the regulation of seizures, equating with the theory of changes in brain waves during sleep observed with the decrease in delta activity and the increase in theta activity, which can be partially explained with the mechanisms of retinoic acid in the signaling of the mesolimbic dopaminergic pathways (Fig. **2**) [45-47].

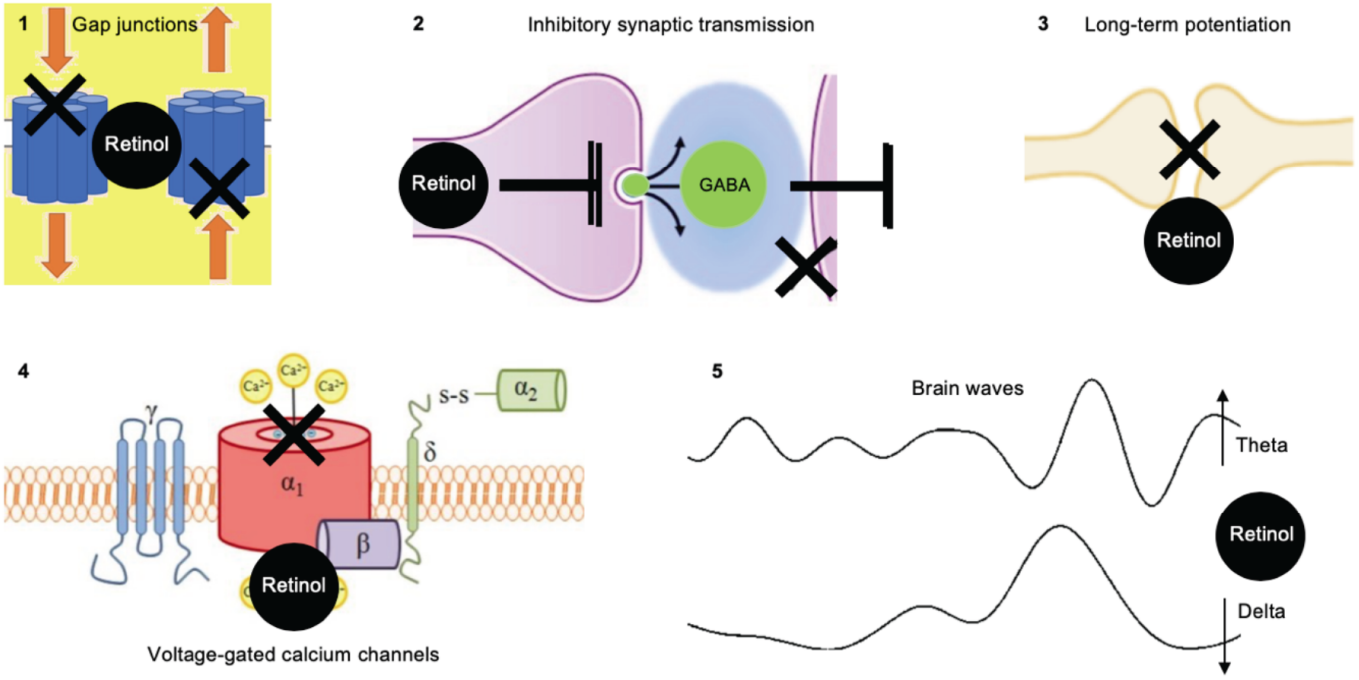

Fig. (2). Main mechanisms of retinol in seizures (**1**) Gap junctions: retinoic acid is a gap junction blocker. (**2**) Inhibitory synaptic transmission: significant reduction of inhibitory synaptic transmission. (**3**) Long-term potentiation: retinoic acid treatment blocks expression of long-term potentiation. (**4**) Voltage-gated calcium channels: retinoic acid inhibits neuronal voltage-gated calcium channels. (**5**) Electroencephalography findings: decreased delta and increased theta activity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.3. Long-term Potentiation

Long-term potentiation is one of the models of memory formation in mammals. It is proposed as a mechanism of plasticity formation in synapses [48]. This memory formation model shares many similarities with the kindling epilepsy model. Memory is known to be altered as a consequence of seizures. One of the similarities of these two models is that for the generation of both memory and epileptic activity, a high frequency of neuronal activity is required, both models are more easily carried out with high-frequency stimuli, through the facilitation of the synapse formation and sharing biochemical mechanisms such as the protein formation of the n-methyl-d-aspartate receptor (NMDA) generated by calcium signaling. The participation of the hippocampus in the generation of new memories and its low threshold to be a generator of seizures in the brain are known [49-51]. On the other hand, it is known that the administration of retinoic acid inhibits long-term potentiation (Fig. **2**). Post-synaptic entry induced by AMPAR retinoic acid requires activation of NMDAR, exocytosis generated by AMPAR retinoic acid requires syntaxin-4, while long-term potentiation involves syntaxin-3, and complexin binding to vesicles that affects AMPAR inhibits exocytosis generated by retinoic acid [52, 53].

5.4. Voltage-gated Calcium Channels

Voltage-dependent l-type and non-l-type calcium channels can be inhibited by retinoic acid, both are affected by retinoic acid, demonstrating retinoid receptors interact with G proteins (Fig. **2**). This information suggests that retinoids may affect synaptic calcium signaling through diverse mechanisms [54-56]. On the other hand, it has been reported that l- type and non-l-type channels are expressed in the life of human teratocarcinoma cell line ntera 2/c1.d1 (nt2-cells) during induction of differentiation by retinoic acid; nt2-cells are a culture model of human neurons. These voltage-dependent Ca^{2+} channels play the main role in regulating intracellular Ca^{2+} homeostasis and excitability of neurons [57].

5.5. Inhibitory Synaptic Transmission

In response to reduced synaptic excitation, retinoic acid signaling plays an important role in regulating inhibitory synaptic transmission. In mouse hippocampal neurons, retinoic acid induces the internalization of GABAa receptors in synapsis, leading to a significant decrease of inhibitory synaptic transmission (Fig. **2**). Retinoic acid acts as an organizer to modify synaptic balance through its capacity to directly modulate excitatory and inhibitory synaptic strength [26, 27, 58].

6. GENETICS AND EPILEPSY

Genetic factors can cause recurrent abnormal mechanisms that produce synchronization and hyperexcitability of neuronal networks. In recent years, several ion channel gene mutations have been associated with idiopathic epilepsies. Meanwhile, most epileptic syndromes are of genetic etiology produced by genes involved in functions as cortical development, mitochondrial function and cell metabolism [59-62]. Tables **1** and **2** summarize the main reports of genes involved in the downregulation and upregulation of neuronal excitability regardless of retinoid acid administration.

7. RETINOID RELATED GENES AND EPILEPSY

An association with genetics and epilepsy has been reported with the loss of function of the retinoid-related nuclear receptor (RORB), resulting in a phenotype that involves intellectual disability and generalized seizures, frequently with absences, nonsense and missense mutations and copy number variants of various sizes involving the RORB gene may give rise to RORB haploinsuffiency. This evidence suggests a novel pathophysiological mechanism for seizure susceptibility, that involves the dysfunction of RORβ

Table 1. Neuronal excitability genes downregulated.

Gene	Implied Function	Refs.
IDH1	A recent meta-analysis identified that an IDH1 mutation was correlated to a higher preoperative seizure incidence in LGG (low-grade gliomas).	[63]
HBP1	The HBP1 gene is decreased in epileptogenesis and has been linked to developmental seizures.	[64]
MLLT3	A case report of a constitutional translocation t(4;9)(q35;p22) disrupting the AF9/MLLT3 gene in a girl with neuromotor development delay, cerebellar ataxia and epilepsy was described. Array-CGH analysis at 1 Mbase resolution did not reveal any additional deletions/duplications. The authors hypothesize a loss-of-function mutation of the AF9/MLLT3 gene, and a possible role for the FAT gene on chromosome 4, in the genesis of the proband's severe neurological phenotype.	[65]
WNT5A	The loss of Wnt5a results in cerebellar hypoplasia and depletion of GABAergic and glutamatergic neurons. Besides, Purkinje cells display stunted, poorly branched dendritic arbors. WNT5A has been found to be present in hypoxic seizure models.	[66, 67]
KMT2E	KMT2E has been linked to neurodevelopmental disorder on the basis of 38 individuals in 36 families. Epilepsy was present in about one-fifth of individuals with truncating variants and was responsive to treatment with anti-epileptic medications in almost all. More than 70% of the individuals were male, and expressivity was variable by sex; epilepsy was more common in females and autism was more common in males.	[68]
AHSP	In a recent study, AHSP was found to be present in various epilepsy groups and is believed to play a role in the molecular progress of epilepsy.	[69]

Table 2. Neuronal excitability genes upregulated.

Gene	Implied Function	Refs.
SLC38A1	May supply glutamatergic and GABAergic neurons with glutamine which is required for the synthesis of glutamate and GABA.	[70]
HPCAL1	The protein encoded by this gene is a member of the neuron-specific calcium-binding proteins family found in the retina and brain. It may be involved in the calcium-dependent regulation of rhodopsin phosphorylation and may be of relevance for neuronal signaling in the central nervous system.	[71]
CCND2	Adult mice with a mutation in the cell cycle regulatory gene Ccnd2, encoding cyclin D2, lack newly born neurons in the dentate gyrus of the hippocampus and in the olfactory bulb. In contrast, the genetic ablation of cyclin D1 does not affect adult neurogenesis.	[72]
PRTG	Associated with the development of various tissues, especially neurogenesis. PRTG is a potential novel recessive epilepsy gene and thus, compound heterozygous variants should be considered in sporadic epilepsy.	[73, 74]
FUT4	CD15 is a fucosyl moiety (specifically, 3-fucosly-N-acetyl-lactosamine) that is a posttranslational modification of some surface proteins. The enzyme responsible for this process is fucosyltransferase 4 (FUT4). A recent study observed a dramatic reduction in the incidence of status epilepticus and subsequent spontaneous convulsions as monitored visually or electroencephalographically in Fut−/− mice.	[75, 76]
LHX1	After kainate-induced seizures, Lhx1 mRNA presents a significant increase over very low baseline expression in all the hippocampal fields in response to seizures.	[77]
CSNK2A1	Patients with CSNK2A1 variants showed mild to profound intellectual disabilities, developmental delays, and various types of seizures. Previous studies have found a total of 20 CSNK2A1 variants in 28 individuals with syndromic intellectual disability.	[78]
TIPARP	Loss of Tiparp resulted in an aberrant organization of the mouse cortex, where the upper layers presented increased cell density in the knock-out mice compared with wild type. Tiparp loss predominantly affected the correct distribution and number of GABAergic neurons.	[79]
SLC2A1	The classic form of SLC2A1 mutations is associated with epileptic encephalopathy and complex movement disorders, whereas milder forms are described with primary movement disorders and other paroxysmal symptoms.	[80]
CCND2	The clinical diagnosis of Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH) syndrome can be established in individuals with the two core features: megalencephaly and bilateral perisylvian polymicrogyria. The molecular diagnosis of MPPH syndrome is established in a proband with some of the suggestive clinical and imaging features and the identification of a heterozygous pathogenic variant in one of three genes: AKT3, CCND2, or PIK3R2. MPPH syndrome is a disorder characterized by the presence of multiple birth defects and developmental delay. Classic signs and symptoms include polymicrogyria, megalencephaly, seizures, polydactyly, and hydrocephalus.	[72, 81]
PRICKLE1	Mutations in the PRICKLE1 gene alter the structure of prickle homolog 1 and disrupt its ability to interact with other proteins. However, it is unclear how these changes lead to movement problems, seizures, and the other features of PRICKLE1-related progressive myoclonus epilepsy with ataxia.	[82]

and associated pathways, resulting in hyperexcitability of neurons [83, 84].

In the chromosome 17p11.2, a reciprocal microdeletion and microduplication are related with Smith-magenis (SMS) and potocki-lupski syndromes. In humans, the retinoic acid induced 1 (RAI1) is the gene responsible for most phenotypes in SMS [85]. The RAI1 gene contains 6 exons, of which exon 3 encodes a 1,906 amino acids RAI1 protein [86]. The RAI1 gene is believed to function as a transcription factor, found in the presence of a bipartite nuclear localization signal and a zinc finger-like plant homeodomain that is preserved in the trithorax group of chromatin-based transcription regulators. The RAI1 promotor region encloses several binding sites for regulation, involving a retinoic acid-responsive element [87]. Experimental and clinical studies suggest that RAI1 is likely the dosage-sensitive gene responsible for most clinical phenotypes, some of which include seizures [88].

The retinoid-related orphan alpha gen (RORα) and its nuclear receptor are essential for cerebellar development [89]. The RORα gene is present on chromosome 15q22.2 and spans a 730 kb genomic region comprising 15 exons [90]. Copy-number variant deletions, duplications and mutations involving RORα have been described in patients from families with seizures, intellectual disability, autistic features and cerebellar ataxia [91].

CONCLUSION

In summary, retinoids play important and diverse functions throughout the brain. Regarding epilepsy, after our review of current published literature, we conclude that the antiepileptogenic effect of retinoids is based on modulation

of gap junctions, neurotransmitters, long-term potentiation, calcium channels and several other genes associated to retinoids. As we mentioned before, retinoids were developed as potential agents for medical use. The antiepileptogenic effect of retinoic acid is an important opportunity for further research which will allow us to better understand the mechanisms involved. Considering this, future research, including the design of a first clinical trial, regarding the possible use of synthetic retinoids to treat seizures is warranted.

LIST OF ABBREVIATIONS

AMPA	=	a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
at-RA	=	All-trans-RA
CRABPs	=	Cellular Retinoic Acid-Binding Proteins
CRBPs	=	Cellular Retinol-Binding Proteins
ERABP	=	Epididymal Retinoic Acid-Binding Protein
FUT4	=	Fucosyltransferase 4
GLUR1	=	Subunit Glutamate Receptor 1
LGG	=	Low-Grade Gliomas
MPPH	=	Megalencephaly-Polymicrogyria-Polydactyly-Hydrocephalus
NMDA	=	N-Methyl-D-Aspartate
NT2-cells	=	Human Teratocarcinoma cell line Ntera 2/C1.D1
RAI1	=	Retinoic Acid Induced 1
RAR	=	Retinoic Acid Receptors
RAREs	=	Retinoic Acid Response Elements
RBP	=	Retinol-Binding Protein
RORB	=	Retinoid-Related Nuclear Receptor
RXRs	=	Retinoid X Receptors
SMS	=	Smith-Magenis Syndrome

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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