The Role of Retinoids in the Adult Nervous System and their Therapeutic Potential

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Abstract: The mode of action of retinoids in relation to their activity in the adult central nervous system and the potential of synthetic retinoid analogues is reviewed. Investigation into the activity of such molecules will further our understanding of the retinoid pathway during nervous system development and in various neurological disease states.

Key Words: Vitamin A, retinoids, adult nervous system, development, neurological disorder, synthetic retinoid, therapeutics.

INTRODUCTION

In 1960, the International Union of Pure and Applied Chemistry – International Union of Biochemistry (IUPAC-IUB) recommended the nomenclature of the three parent vitamin A compounds to be retinol, retinal and retinoic acid. By 1982, IUPAC-IUB had defined the term vitamin A as 'The generic descriptor for retinoids exhibiting qualitatively the biological activity of retinol,' and a retinoid as 'a class of compounds consisting of four isoprenoid units joined in a head-to-tail manner, formally derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional group at the terminus of the acyclic portion'. This nomenclature is still in part used today and incorporates both natural and synthetic analogues of retinol. The correct structure for retinoic acid (*all-trans*) (ATRA) was proposed in 1931 [1].

Natural retinoids are essential for all chordates, being involved in a wide variety of processes during embryogenesis and adulthood. In humans, vitamin A deficiency (VAD) is characterised by xerophthalmia (dry eyes), night blindness and impaired immune responses which, in clinical cases, can prove fatal. VAD is largely associated with developing countries where vitamin A fortified or rich foods are in poor supply. According to a report by the World Health Organisation (WHO) in 1995 [2], VAD is a public health problem in over 120 countries. Over 1 million childhood deaths are associated with VAD annually and 3 million people are said to be clinically vitamin A deficient. However, excessive dietary or therapeutic intake of vitamin A (Hypervitaminosis A) can also give rise to a range of problems associated with skin, nervous system, circulation, bone formation and immune system and malformations of the foetus [3]. Both of these conditions indicate the importance of the close regulation of retinoic acid up-take and metabolism.

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As retinoids are able to penetrate the central nervous system (CNS), an excess or deficiency can prove detrimental to normal mental development, being linked to various disorders such as retardation and depression. This review briefly summarises work on retinoid function and biochemical pathways, and focuses on the roles of retinoic acid and its isomers in normal and abnormal adult neural regulation and differentiation. It also covers the potential therapeutic applications of synthetic retinoid compounds for numerous neurological disorders.

RETINOID FUNCTION

One of the earliest discoveries of a specific retinoid function was in 1968 [4], when it was discovered that 11-cis-retinal was the chromophore component of the photoreceptors in the visual cycle. Since then, however, retinoids have been found to play essential roles in numerous biological processes, including vision [4], reproduction [5], immune competence [6], cellular regulation and differentiation in post-natal and adult organisms [7, 8] and embryonic growth and development [9].

The importance of vitamin A during embryonic development was exemplified in studies of VAD and hypervitaminosis A during pregnancy. Both conditions resulted in embryonic/foetal malformations ranging from disorders of the skin, nervous system, and immune system (for a detailed review see Blomhoff and Blomhoff 2006 [10]). This need for a very defined and regulated concentration of retinoids during embryogenesis fitted with the discovery that ATRA was a potent morphogen during embryogenesis [11], involved in limb formation, body axis orientation and dorsal/ventral patterning of the CNS in vertebrates.

VITAMIN A INTAKE AND STORAGE

Vitamin A cannot be synthesised by any animal species, and is obtained through diet, either in the form of pro-vitamin A carotenoids (such as β-carotenoid) from plants or pre-formed vitamin A, usually in the form of retinyl esters, from eating animal products (stores of ingested vitamin A). Once digested, all of these compounds are re-esterified, *via* enzymatic action, in the intestinal lumen and mucosa, and

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then packaged into chylomicrons and transported to the liver. The liver is the major site for storage and processing of these compounds within the body [12]. Much of the retinol is stored as retinyl palmitate, which is formed after reversible enzymatic activity. When required, retinol is secreted from the liver and transported around the vascular system bound to retinol binding protein (RBP) [13].

Circulating retinol is aided across the cytoplasmic membrane by the retinol binding protein receptor [14]. Once retinol has entered the cell cytosol it can either be stored locally for future use (as retinyl esters) or be converted into forms that activate certain cellular biochemical pathways leading to a modulation of gene transcription Fig. (**1a**).

The predominant active retinoid in the body is ATRA. ATRA is created from retinol *via* a two step reaction. Retinol is oxidised to retinal, catalysed by retinol dehydrogenases (ROLDH), then retinal is oxidised to ATRA catalysed by retinal dehydrogenases (RALDH) [12], see Fig. (**1b**). The storage or breakdown of retinol occurs within the cytosol due to the presence of proteins which bind it with high affinity, called cellular retinol binding protein I (CRBP-I) and cellular retinol binding protein II (CRBP-II). CRBP-I is ubiquitously expressed throughout the organism, and appears to facilitate cellular uptake and metabolism of retinol into either its storage or active forms. CRBP-II is exclusively found in the villi of enterocytes where it is involved in the conversion of retinol into retinyl esters for chylomicron export to the liver [15]. Within some cells there are also cellular retinoic acid binding proteins I and II (CRABP-I and CRABP-II). CRABP-I is involved in the storage of free ATRA, thereby inhibiting the biological activity of the metabolite [16]. Generally, it has been found that cells containing CRABP-I do not respond to ATRA. The role of CRABP-II is less well understood, though it has been hypothesised that it aids the transport of ATRA to its receptors thereby sensitising cells to ATRA [17]. The tissue specific expression of these important retinoid regulators indicates their complex nature of action and involvement in many biological processes.

RETINOIC ACID RECEPTORS

Retinoids elicit biological activity *via* retinoic acid receptors (RAR) which are located in the nuclear envelope. The molecular action of retinoic acid and RARs was first hypothesised during studies of steroid and thyroid hormone action [18]. It was thought that retinol entered the cell, was converted to ATRA *via* enzymatic action and was transported to the nucleus by CRABP-II, where it bound with high affinity to retinoic acid receptors *via* a ligand binding domain. This interaction would lead to a conformation change to the receptor-ligand complex, enabling the binding of a specific retinoic acid response element (RARE) of a

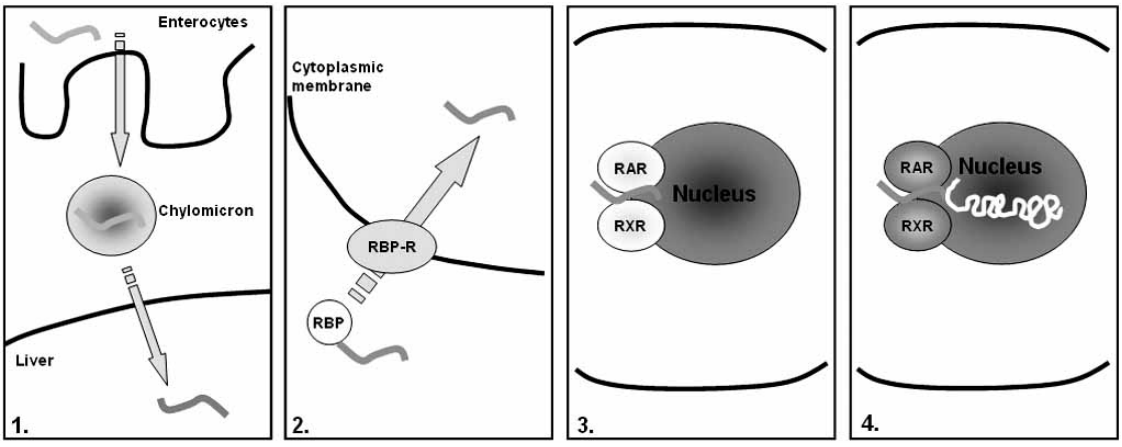


Fig. (1A). Overview of retinoid action. **1:** Ingested retinoids are converted to all-trans-retinol in the intestinal lumen and mucosa by enzymatic action. All-trans-retinol is then packaged into chylomicrons and transported to the liver, which is the major site for storage and processing of this compound. Much of the retinol is stored as retinyl palmitate, which is formed after reversible enzymatic activity. **2:** All-trans-retinol is transported around the vascular system bound to retinol-binding protein (RBP), and accesses target cells via the retinol binding protein receptor (RBP-R). **3:** The retinoid binds to the nuclear retinoic acid receptors (RAR & RXR) which act as signal transducers. **4:** Activated ligand/receptor complexes modulate gene expression by binding to specific retinoic acid response elements (RARE) located in the regulatory regions of target genes.

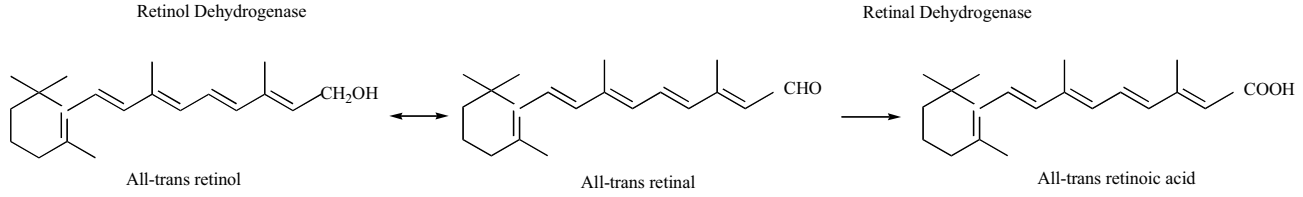


Fig. (1B). Retinol is converted to the active form 'all-trans retinoic acid' via a two step reaction. Retinol is first reversibly converted to retinal, catalysed by retinol dehydrogenase. Secondly, retinal is irreversibly converted to all-trans retinoic acid, catalysed by retinal dehydrogenase.

target gene *via* the DNA-binding domain Fig. (**2**). The first nuclear retinoid receptor was independently discovered by two groups in 1987, now known to be RAR-α1 [19, 20]. RARs can be divided into three sub-groups, RAR-α, RAR-β and RAR-γ, which in turn can be sub-divided into multiple receptor isoforms (i.e. RAR-β1, RAR-β2 and RAR-β3). This heterogeneity is due to the fact that a separate gene that has multiple promoters encodes each subtype, and the products are also able to undergo differential splicing. The complexity of retinoid action is further complicated with the discovery of other nuclear receptors that also exhibit affinity for retinoids. These were termed retinoid X receptors (RXRs) [21]. RXRs could also be divided into three isoforms RXR-α, RXR-β, and RXR-γ. RARs always bind to DNA as heterodimers, pairing up with an RXR. The RXRs are able to act as homodimers or heterodimers, pairing up with themselves, RARs or other receptor compounds [22]. The RARs have the highest affinity for ATRA whereas the RXRs have higher affinity for other retinoids such as 9-cis-retinoic acid (9-cisRA) [23]. The tissue expression of these numerous RAR and RXR subtypes and isoforms varies greatly throughout the organism, again an indication of the complex and varied role the retinoids play in adult and embryonic cell systems.

RETINOIDS AND CNS DEVELOPMENT IN THE EMBRYO

Experiments on retinoid function within the embryonic CNS are extensive and outside the scope of this review, and shall therefore only be summarised briefly (for a recent review see Clagett-Dame and DeLuca, 2002 [24]). Multiple experiments have been carried out verifying the presence of retinoids in the developing CNS of embryos. High-performance liquid chromatography (HPLC) was carried out on mouse embryo extracts at day 10.5 and day 13 and proved the presence of ATRA in the CNS. Endogenous ATRA was mainly found in the spinal cord, with much lower and decreasing amounts found in the hindbrain, midbrain and forebrain, respectively [25]. However, ATRA cannot be synthesised by the neural tube itself at these time points, as it contains no RALDH to catalyse its formation from retinal. RALDH activity is, however, found in the neighbouring paraxial mesoderm, and may enter the neural tube *via* passive diffusion. It is thought that ATRA may act in a paracrine fashion, patterning the dorsal/ventral CNS axis *via* pathways activated at specific positions along the ATRA concentration gradient [26]. Throughout spinal cord development, ATRA expression becomes less uniform and localises where the

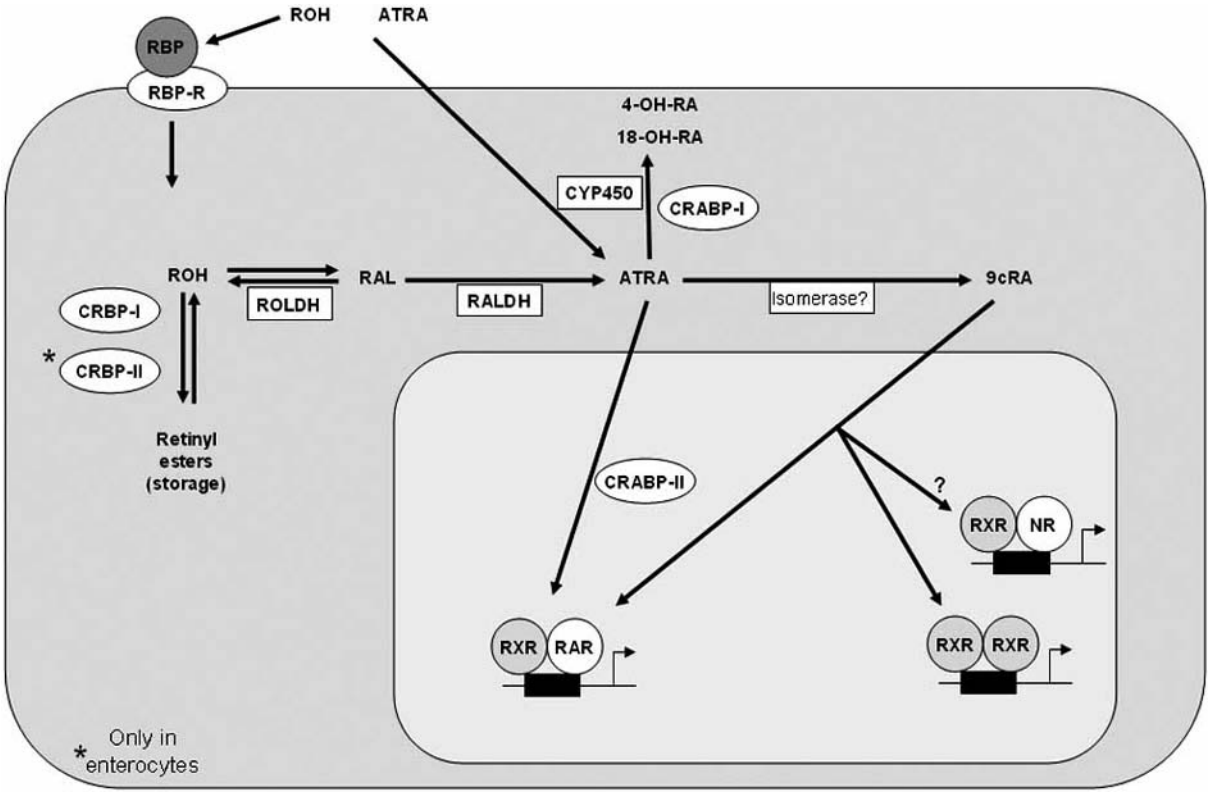


Fig. (2). General overview of retinoid action. Retinol enters the cell via the retinol binding protein receptor and once in the cell is bound to cellular retinol binding proteins (CRBP I & II). These proteins aid either the breakdown of retinol for storage into retinyl esters, or the conversion to all-trans retinoic acid (ATRA). ATRA can be metabolised to more polar molecules catalysed by the CYP450 enzymes and cellular retinoic acid binding protein I (CRABP-I). Cellular retinoic acid binding protein II (CRABP-II) is thought to be involved in the delivery of ATRA to the nuclear envelope where it binds to the retinoic acid receptors (RARs). ATRA has high affinity for the RARs whereas other natural retinoids such as 9-cis retinoic acid (9-cisRA) has high affinity for the retinoid X receptors (RXRs). Once bound to the receptors the ligand/ receptor complex undergoes a conformational change rendering it active, and allows the binding of retinoic acid response elements (RAREs) of target genes.

limb buds form and where motor neurons are concentrated that service the limbs [27].

RETINOIDS AND THE ADULT CNS

Much of the early research into retinoid modes of action focussed on the role of retinoids during embryonic neural development. This was due to the fact that ATRA is known to induce and regulate differentiation in many cell types, not a role which was thought to be required in the adult neural system. However, since the discovery that discrete areas of proliferative cells are present in the adult brain, the study of retinoids has revealed an important regulatory role of these compounds within the adult CNS. The ability of retinol to cross the blood/brain barrier was demonstrated in studies which localised CRBP and RBP binding sites in the blood capillary endothelium and in the epithelial cells of the choroid plexus respectively [28]. The presence of several members of the RALDH enzyme family within the adult brain itself also indicated its ability to synthesise the active retinoid ATRA [29, 30]. It was demonstrated that specific areas of the brain synthesised ATRA, namely the basal ganglia, olfactory bulbs, hippocampus and auditory afferents, all areas that are known to undergo active remodelling of neural connections throughout adulthood. *In-situ* hybridisation studies showed a close correlation between this apparent ability to synthesise ATRA and the presence of CRBP-I, the compound that facilitates the conversion of retinol into active ATRA [31]. Further studies used radio-labelled retinol administered to VAD rats. Ten hours post injection, brain areas were harvested and radioactivity detected. The highest amount of activity was found in the hippocampus-cortex with the lowest being detected in the cerebellum. The radiolabel tag was found to be connected to ATRA not retinol, again indicating the ability of cells in the adult CNS to convert retinol to ATRA [32]. The high levels of ATRA and associated proteins in the hippocampus, specifically the dentate gyrus, strongly implied the involvement of these molecules in region-specific neurogenesis. It was revealed that ATRA contributed significantly to neuronal differentiation within the dentate gyrus, being involved at a very early stage throughout this process [33]. Areas which are non-responsive, therefore sensitive to ATRA in the brain, have been shown to express specific enzymes, such as the cytochrome P450 enzymes P450RA-1 and P450RA-2, which inactivate ATRA by metabolizing the compound to more polar metabolites, including 4-oxo-, 4-hydroxy-, (4-OH-) and 18-hydroxy-(18-OH-) ATRA. These enzymes have been localised to the pons and the cerebellum, areas known to be unresponsive to ATRA stimulation [34, 35]. These experiments all indicate that ATRA is an important regulatory molecule within the adult CNS and interference of these pathways can result in neurological disorders. More evidence indicating the regulatory role of retinoids in the adult CNS is discussed below.

RETINOIDS AND THE HIPPOCAMPUS (INVOLVEMENT IN LEARNING AND MEMORY)

As mentioned above, the hippocampus is an area of the adult brain with known neuronal plasticity. This remodelling of neural connections is the underlying process involved in episodic, declarative and spatial learning and memory establishment. Retinoic acid has been found to play a regulatory role in this long term potentiation (LTP) and long term depression (LTD) processes involved in this neuronal plasticity within the hippocampus [36]. Investigations into VAD revealed a significant deficit in spatial learning and memory in rats deprived of vitamin A. As little as 12 weeks of dietary deficiency was enough to induce these deficits, which upon re-introduction of vitamin A into the diet were reversed [37]. Other studies have shown a more permanent reduction in the expression of RAR-β and RARβ/γ receptor subunits after 31 weeks deficiency [38]. These studies all support the theory that retinoids are involved in the signalling pathways leading to higher cognitive functions.

RETINOIDS IN NEUROLOGICAL DISORDERS (SCHIZOPHRENIA, ALZHEIMER'S AND MOTOR NEURON DISEASE)

The retinoic pathway is becoming a key focus in many studies looking at neurological disorders. As with the embryonic regulation of the retinoid signalling pathway, any deviation from optimal levels appears to induce neurological dysfunctions. Recent papers have linked the addition of retinoic acid to the alleviation of oxidative stress-induced neuronal death in specific areas of the adult brain, namely those involved in cognition and conditions such as depression, Alzheimer's and Parkinson's disease [39-42]. These data, and those discussed below, indicate the importance of this particular pathway in optimal brain management, and hint at future therapeutic remedies in the control or treatment of this group of disorders.

Schizophrenia

One such area where retinoic acid dysregulation appears to be involved in the diseased state is schizophrenia. The learning and memory pathways of the hippocampus are selectively impaired in schizophrenia, so it would stand to reason that retinoic acid pathway abnormalities could be involved in this disease. Many reports eluded to retinoid dysfunction as one of a number of causative factors for schizophrenia (for a review see Goodman, 1998 [43]). More recent experiments show concrete evidence of this effect. A decrease in RXR signalling is seen in some schizophrenia patients [44] and the administration of natural RXR agonists such as Docosahexaenoic acid (DHA) can overcome some symptoms [45]. Comparisons of normal and schizophrenia brain section expression of RARs indicated a two-fold increase of RAR-α in the dentate gyrus of the schizophrenia sections [46]. Proteomic evaluation of body fluids from schizophrenia patients versus mentally healthy controls indicated a significant down-regulation of transthyretin (TTR) and apolipoprotein E (ApoE) in the cerebrospinal fluid. Both proteins are associated with the transport of retinol around the body and brain, therefore an important step leading to correct retinoid functioning [47]. Potentially, data presented in these studies could signify that an insufficient amount of retinoids are being transported around the brain leading to the abnormal expression levels of retinoid signalling components. It was also noted that, after 2 months treatment with antipsychotic drugs, the plasma expression of TTR tetramer was significantly increased in those patients that were responding to the treatment, indicating that these aberrant expression levels could be rescued [47]. It can be concluded

that the synthesis of specific retinoid compounds/retinoid transporter molecules could be advantageous in the treatment of this disorder and this is discussed in more detail below.

Alzheimer's Disease

Retinoids have also been implicated in Alzheimer's disease (AD), another disease associated with cognitive abnormalities. Although, to date, no specific genes have been linked to AD, genome scans have indicated strong gene linkages, and at these specific loci important genes related to the retinoid pathway are always found [48]. As in the schizophrenia research, some of these retinoid genes have been identified as playing a role in the transport of retinoids [48]. Again, if these transporters are not functioning adequately, or are found in decreased levels, this has the potential to have serious implications for optimal retinoid functioning. Disruption of the retinoid signalling pathway also appears to increase the amount of amyloid β protein in the brain, one of the major components involved in amyloid plaque formation, a major characteristic of AD. In one year old rats that have been VAD since weaning, positive expression for amyloid β protein is seen in the cerebral cortex, compared to negative results in corresponding control samples [49]. In similar *in-vivo* deficiency models, an increase in amyloid plaque formation is seen with a decrease in the expression of the retinoid receptor RAR-β [50], which can be rescued upon re-introduction of vitamin A into the diet. This is consistent with *in-vitro* observations that a high level of retinoic acid is able to protect against the death of hippocampal neurons mediated by amyloid β, another characteristic of AD [51]. All of these studies again indicate the therapeutic potential of retinoids in the control or possible treatment of this disease.

Motor Neuron Disease

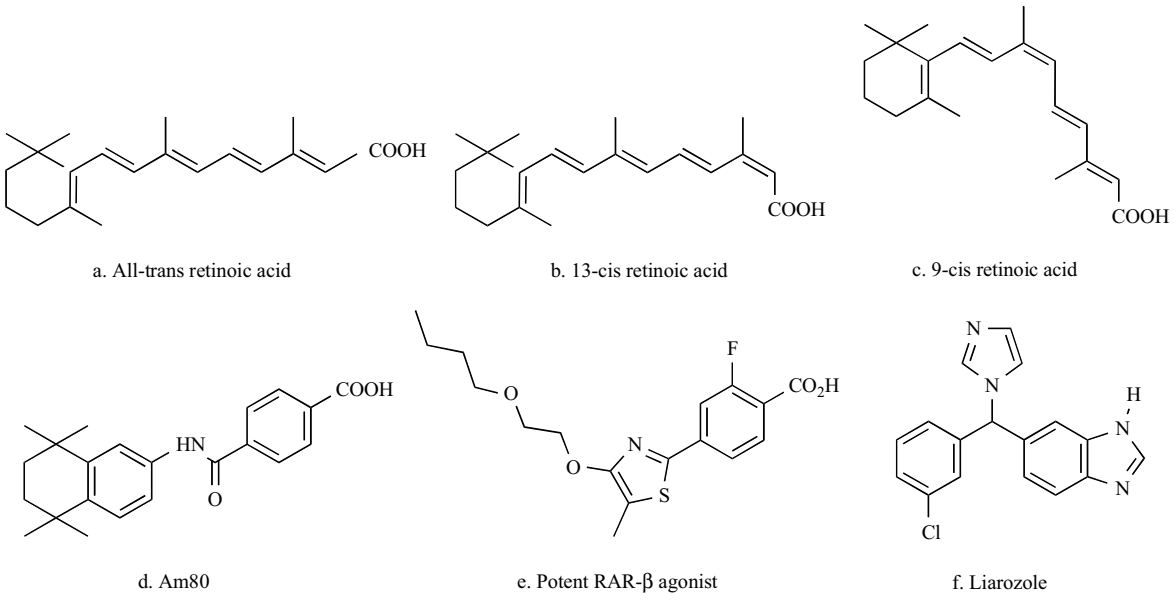
There are many other neurological disorders for which the symptoms are associated with a dysregulation of the retinoid signalling pathway. Another example is motor neuron disease. In this disease, an accumulation of neurofilament and vacuolations in motor neurons followed by motor neuron cell death is characteristic, alongside an increase in astrocytosis. In VAD rat models, these characteristics were noted in samples of motor neurons from the spinal cord, along with a decrease in expression of RAR-α [52]. This study also examined expression patterns in human patients of amyotrophic lateral sclerosis (ALS). They showed a decrease in the total number of RAR-α positive neurons and a decrease in RALDH-2 positive neurons compared to control samples, and in the motor neurons that were left, there was a decrease in expression of both of these transcripts. Other studies examined whether there was a difference in serum levels of retinol between ALS patients and age-matched healthy controls. Using HPLC, the authors concluded that there was no significant difference between the healthy and diseased groups [53]. When combined, these studies lead to the conclusions that motor neuron disease is in part a consequence of retinoid signalling malfunctions and not in general due to a deficiency of vitamin A. Again, it appears that the transport of the retinoid is defective, leading to an aberrant expression of the receptors involved. It is yet to be established whether motor neuron cell death can be rescued *via* some form of retinoid therapy.

NOVEL RETINOID COMPOUNDS AS A THERAPY FOR NEUROLOGICAL DISEASES AND CANCER

As alluded to above, there is evidence that in some neurological disorders, at least in *in-vitro* experiments, symptoms associated with retinoid dysfunction can be overcome with retinoid therapy. The natural retinoids ATRA, Fig. (**3a**), 13-cis-retinoic acid (13-cisRA), Fig. (**3b**) and 9-cisRA, Fig. (**3c**) are already used in some therapy regimes for some cancers and for some dermatological diseases such as acne. For example, ATRA is used with relative success in the treatment of acute promyelocytic leukaemia due to its ability to induce differentiation of the aberrant cell population [54]. However, due to its rapid metabolism and catabolism by the cytochrome P450 enzymes within the body, and serious side-effects after long-term treatment, it is a far from ideal compound. Accutane (containing 13-cisRA) is used for the treatment of acne; however, its use is the subject of serious controversy (summarised in Strahan and Raimer, 2006 [55] and references therein). Some scientific groups have proposed a link between the chronic use of this compound and depression and suicidal tendencies, due to a decrease in hippocampal cell formation (see, for example, Crandall *et al*. 2004 [56]). However, other groups disagree with these findings (see, for example, Jick *et al*. 2000 [57]).

Both of these compounds are pan-RAR activators, and therefore, have the potential to effect numerous different biological processes which could explain the associated debilitating side effects. For example, activation of the RAR-γ receptor sub-types is associated with retinoid skin toxicity side-effects [58]. Much research has focussed on the synthesis of specific and selective RAR agonists and antagonists to use in the treatment of many neurological disorders. The rationale is that these more selective activators of retinoid pathways could overcome the side effects associated with the use of their natural pan-RAR activating counterparts. Whilst there is reference to the chemical production of many thousands of different synthetic retinoids in the literature, there are comparatively few data concerning an in-depth characterisation of their biological activity, let alone their effect on neural cells. One promising study which does show good evidence of biological activity was reported in 2005 [59]. Simoni *et al.* synthesised a number of terphenyl compounds, synthetic retro-retinoid analogues, to try to establish their apoptotic qualities. They discovered that these compounds actually protected promyelocytic HL-60 cells against apoptosis. As many neurological diseases are associated with apoptosis of neurons, i.e. AD, Parkinson's disease, Huntington's disease and motor neuron disease to name a few, the group became interested in this quality. However, they found that the compounds only had modest protective apoptotic activity in neuronal cell lines, but concluded that further study into this group of compounds could be very worthwhile for treatment of neurological disorders.

Another synthetic retinoid which has promising therapeutic potential for a number of different neurological disorders is Am80 (tamibarotene, Fig. (**3d**) [60]). This synthetic retinoid has been shown to rescue scopolamine induced memory-loss in rat model systems [61]; the most effective result was observed when the retinoid was administered in tandem with the rexinoid HX630. In this model system no adverse



a. All-trans retinoic acid b. 13-cis retinoic acid c. 9-cis retinoic acid

d. Am80 e. Potent RAR-β agonist f. Liarozole

Fig. (3). Chemical structures of retinoids (a-e) and a retinoic acid metabolism blocking agents (RAMBAs) compound (f) which are either already being used in therapy regimes for neurological disorders (a, b, c, d, e & f) or show promising potential as therapeutic agents (e). a, b, & c are naturally occurring retinoids and d, e, & f are synthetic compounds.

side effects were seen. These data point to the use of these compounds to treat neurological disorders associated with learning deficits such as AD. Human clinical trials of Am80 have already been carried out in other fields, investigating Am80 as a possible treatment for APL. As mentioned above, ATRA is the main drug of choice for this disease; however, in patients who relapse from complete remission after ATRA therapy, a second course of this drug is relatively ineffective. In one study, patients who had relapsed were treated with Am80 and 58% achieved complete remission. As Am80 is an agonist for only RAR-α and RAR-β, milder side effects were observed with this compound [62]. Again, this established specificity can be seen as advantageous in the treatment of many neurological disorders.

More specific agonists of the RARs have also been developed. Using their novel cell-based assay R-SAT, Piu *et al.* identified a variety of selective RAR compounds [63], the most interesting being a potent RAR-β2 agonist, Fig. (**3e**), that distinguishes between the different RAR-β sub-types [64]. This particular sub-type has been shown to be very important in the neurite out-growth of the embryonic spinal cord, and is absent in adult spinal cord sections. When it was transfected into neurons of the spinal cord from adult rats and mice, neurite outgrowth was observed *in-vitro* [65]. This receptor sub-type has also been associated with the dopamine signalling pathway [66]. Dysregulation of this pathway is seen in some neurological disorders, for example Parkinson's disease and schizophrenia; therefore, this agonist may have potential utility as a treatment for these types of neurological disorders.

The synthesis of molecules with higher cytotoxic activity on cancer cells and increased water solubility improves their ability to act as chemotherapeutic and chemopreventative agents. Novel synthesis approaches and biological evaluations of the products are producing compounds which appear to be exciting new procancer drugs [67].

Other areas of retinoid research have focussed on the development of compounds which will enhance the therapeutic potential of already available retinoid compounds. For example, in order to overcome the rapid breakdown and sensitizing of ATRA by the body after use as a therapeutic treatment, retinoic acid metabolism blocking agents (RAMBAs) have been developed. These compounds elicit a response by inhibiting the P450 enzymes, namely CYP enzymes, which catabolises ATRA (for a recent review see Njar *et al.* 2006 [68]). The most studied RAMBA is Liarozole, Fig. (**3f**), developed by the Janssen Research Foundation [69]. In 2004, Liarozole was granted orphan drug designation by the U.S. Food and Drug Administration for the treatment of congenital ichthyosis (a severe dermatological disorder) and has also been granted orphan drug status by the European Commission. This is a good example of how manipulation of the retinoic acid signalling pathway can be key to the treatment of certain related diseases.

CONCLUSIONS

Retinoids have been demonstrated to be powerful regulators of neural differentiation and regulation both within embryonic development and adult brain functioning. They elicit biological activity by binding to specific receptors located within the nuclear envelope. Activation of these receptors results in a mediation of specific gene expression. A dysfunction in this pathway leads to many abnormalities in embryonic development and is shown to be associated with numerous neurological disorders within the adult. The natural retinoids are involved in the treatment programmes for many different disorders; however, their utility is limited due to the rapid breakdown of the compounds within the body and debilitating side effects associated with their long-term

use. To overcome these problems, novel retinoid compounds have been synthesised which are much more receptor-specific. The limited biological activity data available suggests that these compounds are as potent as their natural counterparts, but it remains to be seen whether they overcome the side effects.

It appears that the dysregulation of the retinoid pathway in the neurological disorders discussed above often results from a defect in the transport of retinol into the cells in question. It would be of interest to investigate synthesising more efficient novel retinoid transporter molecules, which could lead to an increase in retinoid availability. This approach could provide an improved method of treatment/management for these debilitating diseases.

ABBREVIATIONS

IUPAC-IUB	=	International Union of Pure and Applied Chemistry-International Union of Biochemistry
ATRA	=	*All-trans*-retinoic acid
VAD	=	Vitamin A deficiency
WHO	=	World Health Organisation
CNS	=	Central nervous system
RBP	=	Retinol binding protein
ROLDH	=	Retinol dehydrogenase
RALDH	=	Retinal dehydrogenase
CRBP-I	=	Cellular retinol binding protein I
CRBP-II	=	Cellular retinol binding protein II
CRABP-I	=	Cellular retinoic acid binding protein I
CRABP-II	=	Cellular retinoic acid binding protein II
RAR	=	Retinoic acid receptor
RARE	=	Retinoic acid response element
RXR	=	Retinoid X receptor
9-cisRA	=	9-cis-retinoic acid
HPLC	=	High performance liquid chromatography
LTP	=	Long term potentiation
LTD	=	Long term depression
DHA	=	Docosahexaenoic acid
TTR	=	Transthyretin
ApoE	=	Apolipoprotein E
AD	=	Alzheimer's Disease
ALS	=	Amyotrophic lateral sclerosis
13-cisRA	=	13-cis-retinoic acid
RAMBAs	=	Retinoic acid metabolism blocking agents

REFERENCES

[1] Karrer, P.; Morf, R.; Schoepp, K. *Helv. Chim. Acta,* **1931**, *14*, 1431.

[2] World Health Organization; *The Global Prevalence of Vitamin A Deficiency*, Geneva, **1995**.

[3] Hathcock, J.N.; Hattan, D.G.; Jenkins, M.Y.; McDonald, J.T.; Sundaresan, P.R.; Wilkening, V.L. *Am. J. Clin. Nutr.,* **1990**, *52*, 183.

[4] Wald, G. *Nature,* **1968**, *219*, 800.

[5] Thompson, J.N.; Howell, J.M.; Pitt, G.A. *Proc. R. Soc. Lond. B. Biol. Sci.,* **1964**, *159*, 510.

[6] Ross, A.C. *Proc. Soc. Exp. Biol. Med.,* **1992**, *200*, 303.

[7] Ng, K.W.; Zhou, H.; Manji, S.; Martin, T.J. *Crit. Rev. Eukaryot. Gene Expr.,* **1995**, *5*, 219.

[8] Mey, J.; McCaffery, P. *Neuroscientist,* **2004**, *10*, 409.

[9] Maden, M. *Proc. Nutr. Soc.,* **2000**, *59*, 65.

[10] Blomhoff, R.; Blomhoff, H.K. *J. Neurobiol.,* **2006**, *66*, 606.

[11] Thaller, C.; Eichele, G. *Nature,* **1987**, *327*, 625.

[12] Quadro, L.; Hamberger, L.; Colantuoni, V.; Gottesman, M.E.; Blaner, W.S. *Mol. Aspects Med.,* **2003**, *24*, 421.

[13] Kanai, M.; Raz, A.; Goodman, D.S. *J. Clin. Invest.,* **1968**, *47*, 2025.

[14] Maraini, G.; Gozzoli, F. *Invest. Ophthalmol.,* **1975**, *14*, 785.

[15] Ong, D.E. *J. Biol. Chem.,* **1984**, *259*, 1476.

[16] Dong, D.; Ruuska, S.E.; Levinthal, D.J.; Noy, N. *J. Biol. Chem.,* **1999**, *274*, 23695.

[17] Budhu, A.; Gillilan, R.; Noy, N. *J. Mol. Biol.,* **2001**, *305*, 939.

[18] Evans, R.M. *Science,* **1988**, *240*, 889.

[19] Giguere, V.; Ong, E.S.; Segui, P.; Evans, R.M. *Nature,* **1987**, *330*, 624.

[20] Petkovich, M.; Brand, N.J.; Krust, A.; Chambon, P. *Nature,* **1987**, *330*, 444.

[21] Mangelsdorf, D.J.; Ong, E.S.; Dyck, J.A.; Evans, R.M. *Nature,* **1990**, *345*, 224.

[22] Kliewer, S.A.; Umesono, K.; Mangelsdorf, D.J.; Evans, R.M. *Nature,* **1992**, *355*, 446.

[23] Levin, A.A.; Sturzenbecker, L.J.; Kazmer, S.; Bosakowski, T.; Huselton, C.; Allenby, G.; Speck, J.; Ratzeisen, C.L.; Rosenberger, M.; Lovey, A.; Grippo, J.F. *Nature,* **1992**, *355*, 359.

[24] Clagett-Dame, M.; DeLuca, H.F. *Annu. Rev. Nutr.,* **2002**, *22*, 347.

[25] Horton, C.; Maden, M. *Dev. Dyn.,* **1995**, *202*, 312.

[26] Maden, M. *J. Neurobiol.,* **2006**, *66*, 726.

[27] McCaffery, P.; Drager, U.C. *Proc. Natl. Acad. Sci. USA,* **1994**, *91*, 7194.

[28] MacDonald, P.N.; Bok, D.; Ong, D.E. *Proc. Natl. Acad. Sci. USA,* **1990**, *87*, 4265.

[29] Dev, S.; Adler, A.J.; Edwards, R.B. *Brain Res.,* **1993**, *632*, 325.

[30] Wagner, E.; Luo, T.; Drager, U.C. *Cereb. Cortex,* **2002**, *12*, 1244.

[31] Zetterstrom, R.H.; Lindqvist, E.; Mata de Urquiza, A.; Tomac, A.; Eriksson, U.; Perlmann, T.; Olson, L. *Eur. J. Neurosci.,* **1999**, *11*, 407.

[32] Werner, E.A.; Deluca, H.F. *Am. J. Physiol. Endocrinol. Metab.,* **2002**, *282*, E672.

[33] Jacobs, S.; Lie, D.C.; DeCicco, K.L.; Shi, Y.; DeLuca, L.M.; Gage, F.H.; Evans, R.M. *Proc. Natl. Acad. Sci. USA,* **2006**, *103*, 3902.

[34] White, J.A.; Beckett-Jones, B.; Guo, Y.D.; Dilworth, F.J.; Bonasoro, J.; Jones, G.; Petkovich, M. *J. Biol. Chem.,* **1997**, *272*, 18538.

[35] White, J.A.; Ramshaw, H.; Taimi, M.; Stangle, W.; Zhang, A.; Everingham, S.; Creighton, S.; Tam, S.P.; Jones, G.; Petkovich, M. *Proc. Natl. Acad. Sci. USA,* **2000**, *97*, 6403.

[36] McCaffery, P.; Zhang, J.; Crandall, J.E. *J. Neurobiol.,* **2006**, *66*, 780.

[37] Cocco, S.; Diaz, G.; Stancampiano, R.; Diana, A.; Carta, M.; Curreli, R.; Sarais, L.; Fadda, F. *Neuroscience,* **2002**, *115*, 475.

[38] Etchamendy, N.; Enderlin, V.; Marighetto, A.; Pallet, V.; Higueret, P.; Jaffard, R. *Behav. Brain Res.,* **2003**, *145*, 37.

[39] Zaidi, S.M.; Banu, N. *Clin. Chim. Acta,* **2004**, *340*, 229.

[40] Ahlemeyer, B.; Bauerbach, E.; Plath, M.; Steuber, M.; Heers, C.; Tegtmeier, F.; Krieglstein, J. *Free Radic. Biol. Med.,* **2001**, *30*, 1067.

[41] de Oliveira, M.R.; Moreira, J.C. *Toxicol. Lett.,* **2007**, *173*, 145.

[42] de Oliveira, M.R.; Silvestrin, R.B.; Mello, E.S.T.; Moreira, J.C. *Neurotoxicology,* **2007**, Epub ahead of print.

[43] Goodman, A.B. *Proc. Natl. Acad. Sci. USA,* **1998**, *95*, 7240.

[44] Arvindakshan, M.; Sitasawad, S.; Debsikdar, V.; Ghate, M.; Evans, D.; Horrobin, D.F.; Bennett, C.; Ranjekar, P.K.; Mahadik, S.P. *Biol. Psychiatry,* **2003**, *53*, 56.

[45] Zanarini, M.C.; Frankenburg, F.R. *Am. J. Psychiatry,* **2003**, *160*, 167.

[46] Rioux, L.; Arnold, S.E. *Psychiatry Res.,* **2005**, *133*, 13.
[47] Wan, C.; Yang, Y.; Li, H.; La, Y.; Zhu, H.; Jiang, L.; Chen, Y.; Feng, G.; He, L. *J. Proteome Res.,* **2006**, *5*, 3213.
[48] Goodman, A.B.; Pardee, A.B. *Proc. Natl. Acad. Sci. USA,* **2003**, *100*, 2901.
[49] Corcoran, J.P.; So, P.L.; Maden, M. *Eur. J. Neurosci.,* **2004**, *20*, 896.
[50] Husson, M.; Enderlin, V.; Delacourte, A.; Ghenimi, N.; Alfos, S.; Pallet, V.; Higueret, P. *Neurobiol. Dis.,* **2006**, *23*, 1.
[51] Sahin, M.; Karauzum, S.B.; Perry, G.; Smith, M.A.; Aliciguzel, Y. *Neurotox. Res.,* **2005**, *7*, 243.
[52] Corcoran, J.; So, P.L.; Maden, M. *J. Cell Sci.,* **2002**, *115*, 4735.
[53] Molina, J.A.; de Bustos, F.; Jimenez-Jimenez, F.J.; Esteban, J.; Guerrero-Sola, A.; Zurdo, M.; Orti-Pareja, M.; Gasalla, T.; Gomez-Escalonilla, C.; Ramirez-Ramos, C.; Guillamon, F.; Arenas, J. *Acta Neurol. Scand.,* **1999**, *99*, 315.
[54] Castaigne, S.; Chomienne, C.; Daniel, M.T.; Ballerini, P.; Berger, R.; Fenaux, P.; Degos, L. *Blood,* **1990**, *76*, 1704.
[55] Strahan, J.E.; Raimer, S. *Int. J. Dermatol.,* **2006**, *45*, 789.
[56] Crandall, J.; Sakai, Y.; Zhang, J.; Koul, O.; Mineur, Y.; Crusio, W.E.; McCaffery, P. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*, 5111.
[57] Jick, S.S.; Kremers, H.M.; Vasilakis-Scaramozza, C. *Arch. Dermatol.,* **2000**, *136*, 1231.
[58] Zelent, A.; Krust, A.; Petkovich, M.; Kastner, P.; Chambon, P. *Nature,* **1989**, *339*, 714.
[59] Simoni, D.; Giannini, G.; Roberti, M.; Rondanin, R.; Baruchello, R.; Rossi, M.; Grisolia, G.; Invidiata, F.P.; Aiello, S.; Marino, S.; Cavallini, S.; Siniscalchi, A.; Gebbia, N.; Crosta, L.; Grimaudo, S.; Abbadessa, V.; Di Cristina, A.; Tolomeo, M. *J. Med. Chem.,* **2005**, *48*, 4293.
[60] Kagechika, H.; Kawachi, E.; Hashimoto, Y.; Shudo, K. *Chem. Pharm. Bull. (Tokyo),* **1984**, *32*, 4209.
[61] Shudo, K.; Kagechika, H.; Yamazaki, N.; Igarashi, M.; Tateda, C. *Biol. Pharm. Bull.,* **2004**, *27*, 1887.
[62] Tobita, T.; Takeshita, A.; Kitamura, K.; Ohnishi, K.; Yanagi, M.; Hiraoka, A.; Karasuno, T.; Takeuchi, M.; Miyawaki, S.; Ueda, R.; Naoe, T.; Ohno, R. *Blood,* **1997**, *90*, 967.
[63] Piu, F.; Gauthier, N.K.; Olsson, R.; Currier, E.A.; Lund, B.W.; Croston, G.E.; Hacksell, U.; Brann, M.R. *Biochem. Pharmacol.,* **2005**, *71*, 156.
[64] Lund, B.W.; Piu, F.; Gauthier, N.K.; Eeg, A.; Currier, E.; Sherbukhin, V.; Brann, M.R.; Hacksell, U.; Olsson, R. *J. Med. Chem.,* **2005**, *48*, 7517.
[65] Corcoran, J.; So, P.L.; Barber, R.D.; Vincent, K.J.; Mazarakis, N.D.; Mitrophanous, K.A.; Kingsman, S.M.; Maden, M. *J. Cell Sci.,* **2002**, *115*, 3779.
[66] Krezel, W.; Ghyselinck, N.; Samad, T.A.; Dupe, V.; Kastner, P.; Borrelli, E.; Chambon, P. *Science,* **1998**, *279*, 863.
[67] Um, S.J.; Kwon, Y.J.; Han, H.S.; Park, S.H.; Park, M.S.; Rho, Y.S.; Sin, H.S. *Chem. Pharm. Bull. (Tokyo),* **2004**, *52*, 501.
[68] Njar, V.C.; Gediya, L.; Purushottamachar, P.; Chopra, P.; Vasaitis, T.S.; Khandelwal, A.; Mehta, J.; Huynh, C.; Belosay, A.; Patel, J. *Bioorg. Med. Chem.,* **2006**, *14*, 4323.
[69] Freyne, E.; Raeymaekers, A.; Venet, M.; Sanz, G.; Wouters, W.; De Coster, R.; Wauwe, J.V. *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 267.

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