ANNUAL REVIEWS

Annual Review of Nutrition

Vitamin A and Retinoic Acid in Cognition and Cognitive Disease

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Annu. Rev. Nutr. 2020. 40:247–72

The *Annual Review of Nutrition* is online at nutr.annualreviews.org

https://doi.org/10.1146/annurev-nutr-122319-034227

Keywords

neuroplasticity, Alzheimer's disease, schizophrenia, autism, aging, hippocampus

Abstract

The history of vitamin A goes back over one hundred years, but our realization of its importance for the brain and cognition is much more recent. The brain is more efficient than other target tissues at converting vitamin A to retinoic acid (RA), which activates retinoic acid receptors (RARs). RARs regulate transcription, but their function in the cytoplasm to control nongenomic actions is also crucial. Controlled synthesis of RA is essential for regulating synaptic plasticity in regions of the brain involved in learning and memory, such as the hippocampus. Vitamin A deficiency results in a deterioration of these functions, and failure of RA signaling is perhaps associated with normal cognitive decline with age as well as with Alzheimer's disease. Further, several psychiatric and developmental disorders that disrupt cognition are also linked with vitamin A and point to their possible treatment with vitamin A or RA.

Contents

1. VITAMIN A METABOLISM AND MOLECULAR ACTION IN THE BRAIN

The brain was not an organ that stood out in the early history of vitamin A research and this remained true up to the 1990s (98). Early studies of deficiency indicated the dependence of the eye, skin, immune and reproductive systems, and developing embryo on vitamin A; however, the effects of vitamin A deficiency (VAD) on the adult brain, with the exception of the medulla, were not apparent (64). Nor is vitamin A in the form of retinol or retinyl esters prominent in the brain, in contrast to tissues such as the eye, which uses vitamin A in its visual pigment. Levels of vitamin A in the brain are similar to those in many other tissues with just moderate vitamin A demands. This knowledge directed vitamin A research away from brain function in the past. However, although the brain is not comparable to the eye in terms of vitamin A content, there is "more than meets the eye" when it comes to function and the brain may be able to utilize lower amounts of vitamin A in a variety of actions.

1.1. Vitamin A Transport to the Brain

VAD: vitamin A deficiency

Diet-derived vitamin A, which is stored as retinyl esters in the liver, is released in a homeostatically controlled fashion to provide a constant source of retinol to cells of the body, including those of the brain. Retinol transport through the blood-brain barrier (BBB) is restricted (116). Levels of retinol and retinyl ester are higher in the brain than in other tissues dependent on retinol, such as skin and testis, and are similar to levels in adipose tissue in the mouse (71). By contrast, other studies do not

show that vitamin A levels in the brain are higher than those in, for instance, the kidney (95, 130). Nevertheless, levels in the brain are generally robust, and one study described high levels of retinol in the rat brain with major differences between the sexes (6). Cerebrospinal fluid (CSF), which, among other functions, transports factors within the brain, contains the same protein duo carrying retinol in plasma, retinol-binding protein 4 (RBP4) and transthyretin (TTR), both of which are synthesized by the CSF-generating tissue, the choroid plexus (33, 36). RBP4 is also present in epithelial cells of the blood vessel walls in the brain that make up the BBB (98). The choroid plexus also expresses the protein that binds to retinol-bound RBP4 and assists in transporting retinol into the cell, stimulated by retinoic acid 6 (STRA6), the knockout of which greatly reduces retinol content in the brain (76). Retinol can also enter cells through passive diffusion aided by the presence of cellular retinol-binding protein 1 (CRBP1) in the cell. CRBP1 is present in the choroid plexus (98) and blood vessel walls in the brain (161), capturing retinol and increasing its influx across the BBB. Note that RBP4 also has a wider distribution in certain brain subregions, implying a role for RBP4 in transporting retinol within the brain itself (19, 52, 80).

RA: retinoic acid

RAR: retinoic acid receptor

RXR: retinoid X receptor

1.2. Vitamin A Function in the Cell

Retinoic acid (RA) is the key to vitamin A and brain function because, for most functions, it is the active metabolite of vitamin A (the steps of vitamin A metabolism are illustrated in **Figure 1**). Indeed, the brain is exceedingly efficient at generating RA compared with other vitamin A–dependent organs (155). Cellular retinoic acid–binding protein 1 and 2 (CRABP1 and CRABP2) maintain solubility of RA, and CRABP2 in particular plays a role in transporting RA into the nucleus (110). RA carries out its primary role in the nucleus, binding to specific retinoic acid receptors (RARs), α, β, or γ, members of the nuclear receptor family of transcriptional regulators (10). RARs are activated by all-*trans* and 9-*cis* isomers of RA and function as heterodimers with the nuclear retinoid X receptor (RXR) subtypes α, β, and γ. RXR is a RA receptor activated by 9-*cis* RA and potentially other endogenous retinoids (83). In general, retinoids refer to the naturally occurring and synthetic analogs of vitamin A. The RAR-RXR heterodimer regulates gene expression by binding to a retinoic acid response element (RARE) of the promoter of target genes. Both types of receptors are present in the central nervous system (CNS), and protein expression has been thoroughly investigated by Krężel et al. (82). In the adult brain, RARα and RARγ are widely distributed, with high protein levels present in both the hippocampus and the cortex, whereas RARβ, RXRα, RXRβ, and RXRγ display a restricted presence (82). In these restricted regions, however, levels can be high; for example, RARβ is strongly expressed in the striatum and hypothalamus (82). The local expression of RAR proteins does not always match that of their messenger RNA (mRNA) transcripts, implying a crucial role for posttranscriptional control in their expression. RA via the RARs has the potential to regulate hundreds of genes directly or indirectly (8, 85). The system is turned off predominantly by the CYP26 group of the cytochrome P450 family of enzymes (141), in particular CYP26B1 (1, 141).

2. THE NEED FOR VITAMIN A AND RETINOIC ACID IN THE HIPPOCAMPUS TO CONTROL NEUROPLASTICITY ESSENTIAL FOR LEARNING AND MEMORY

2.1. Control of Retinoic Acid Synthesis in the Hippocampus

The hippocampus, which is part of the limbic system, is a key site involved in cognition owing to its role in learning and memory (13). It is a highly plastic brain region; it can adapt and change

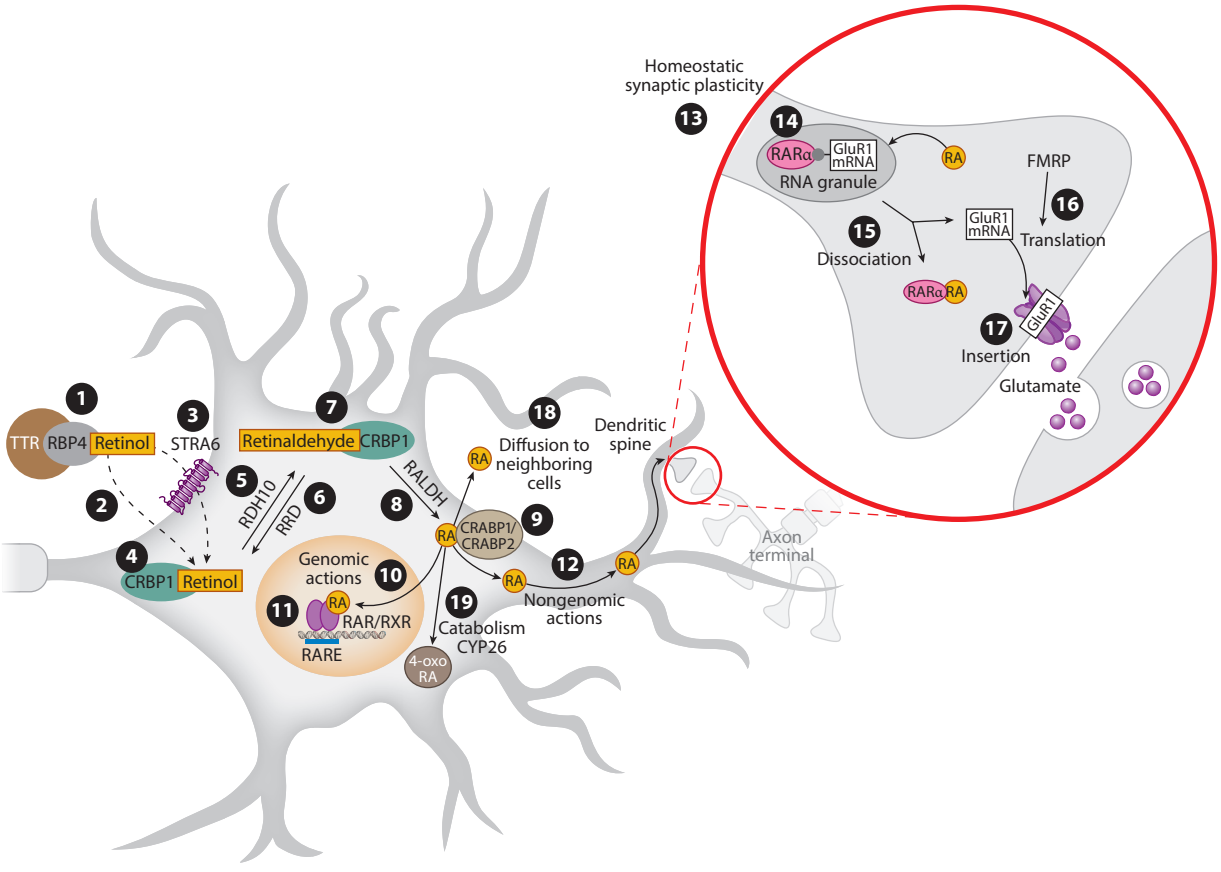


Figure 1

A schematic of vitamin A metabolism in the cell. (*Step 1*) Retinol is delivered to neurons by the RBP4/TTR complex and can enter the cell via (*Step 2*) free diffusion or via (*Step 3*) STRA6. Once inside the cell, (*Step 4*) retinol binds to CRBP1. (*Step 5*) It can then be metabolized to retinaldehyde by retinol dehydrogenases (e.g., RDH10). This step is reversible and retinaldehyde can be (*Step 6*) metabolized back to retinol by RRD. (*Step 7*) Retinaldehyde, bound to CRBP1, can be (*Step 8*) converted to RA by RALDH1, RALDH2, and RALDH3, which are encoded by the genes *ALDH1A1*, *ALDH1A2*, and *ALDH1A3*, respectively (75). Inside the cell, (*Step 9*) RA is bound to CRABP1/CRABP2 to maintain solubility of RA, and (*Step 10*) CRABP2 in particular plays a role in transporting RA into the nucleus (110). (*Step 11*) RA exhibits genomic functions through activation of transcription in the nucleus by binding to RA receptors (RAR-RXR heterodimers) (10). (*Step 12*) RA can also exhibit nongenomic functions, such as (*Step 13*) its involvement in HSP. (*Step 14*) RARα in the cytoplasm is present in mRNA granules, where it binds the mRNA of an ionotropic glutamate receptor subunit (GluR1, which is a subunit for the AMPA-type receptor). (*Step 15*) When RA binds to RARα, GluR1 mRNA disassociates, and in the presence of FMRP it becomes available for (*Step 16*) translation and (*Step 17*) insertion into the membrane. Alternatively, RA (*Step 18*) can diffuse to neighboring cells or (*Step 19*) is removed by catabolism to 4-oxo RA by CYP26A1, CYP26B1, and CYP26C1, with CYP26B1 the predominant form in the brain (1, 141). Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CRABP1, 2, cellular retinoic acid–binding protein 1, 2; CRBP1, cellular retinol-binding protein 1; FMRP, fragile X mental retardation protein; GluR1, glutamate receptor 1; HSP, homeostatic synaptic plasticity; mRNA, messenger RNA; RA, retinoic acid; RALDH, retinaldehyde dehydrogenase; RAR, retinoic acid receptor; RARE, retinoic acid response element; RXR, retinoid X receptor; RBP4, retinol-binding protein 4; RDH10, retinol dehydrogenase 10; RRD, retinal reductase; STRA6, stimulated by retinoic acid 6; TTR, transthyretin.

function in response to the environment. RA is often associated with, and regulates, regions of high neuroplasticity (135). RA signaling in the hippocampus is regulated by the availability of its synthesizing and catabolizing enzymes. In mice, a gradient of RA exists across the infrapyramidal and suprapyramidal blades of the hippocampal dentate gyrus (52) set up by strong expression of RALDH1- and RALDH2-synthesizing enzymes in the meninges and the presence of a CYP26B1-catabolizing enzyme between the blades. This gradient in RA signaling across the dentate gyrus contributes to higher cell proliferation in the infrapyramidal versus suprapyramidal blades. It can be disrupted by inhibition of CYP26B1, resulting in a ratio of cell proliferation between the infrapyramidal and suprapyramidal blades that is closer to 1 (141). That these two blades process information differently likely plays a role in a refined aspect of learning termed pattern separation, and control of cell proliferation and generation of new neurons (neurogenesis) may be incorporated into this type of learning (129). Astrocytes, which provide structural and functional support to surrounding neurons (102), are another potential source of RA for the hippocampus and are the most abundant glial cells in this region. In vivo, astrocytes express low levels of retinaldehyde dehydrogenases (RALDHs); however, in the event that the availability of retinol is low, they can increase protein expression of RA-synthesizing enzymes (133). Astrocytes synthesize and release RA to neurons in a paracrine manner (151). Hippocampal neurons themselves are also proposed to have an activity-controlled autocrine system of synthesis (3). A recent study showing the capacity of RA to correct age-related cognitive decline suggests that the blood directly supplies RA to the hippocampus (37).

LTP: long-term potentiation

LTD: long-term depression

As with much of the initial studies of vitamins, the first phase of research on the brain and vitamin A came from studies of VAD in the adult animal. This approach provided the earliest evidence that vitamin A affects cognition, recognizing, however, that VAD broadly impacts the whole animal, not just the brain. Further, studies of VAD determine the action of not only RA but also vitamin A, because although most effects of vitamin A occur via RA (106), the signaling pathway induced directly by retinol when bound to RBP4 via STRA6 (111) may also influence the brain, which has been little investigated. Studies of VAD in mice are cumbersome because this species has a high capacity for vitamin A storage and induction of VAD requires a prolonged period, up to 40 weeks (40). However, time to deficiency can be shortened by early depletion starting at day 10 of pregnancy (138). Thus, high-quality VAD experiments require a thoughtful understanding of vitamin A biology.

2.2. Retinoic Acid and Neuroplasticity in the Hippocampus: Long-Term Potentiation, Long-Term Depression, and Neurogenesis

Vitamin A is essential for two aspects of neuroplasticity long considered key to learning and memory: long-term potentiation (LTP) and long-term depression (LTD). These processes are the cellular responses that induce lasting changes in synaptic strength, leading to strengthening or weakening of neuronal circuits. The synapse provides the link between each neuron in the circuit, and changes in neuronal circuits are believed to form the substrate of learning and memory. Changes in synaptic strength are quantified by measuring postsynaptic electrical events, which involves measuring the postsynaptic currents (PSCs) that reflect the current passing via cellular ion channels (see the sidebar titled Ion Channels and Neuronal Activity).

VAD in rodents impairs both LTP and LTD in the hippocampus, and the degree of their disruption correlates with the level of retinol deprivation (105). These impairments can be rescued by applying RA or boosting dietary retinol. VAD further compounds the decline in RA signaling because such conditions lead to a decrease in the expression of RARs (RARβ and RXRβ/γ) (40). VAD affects another aspect of neuroplasticity important for learning and memory: neurogenesis.

ION CHANNELS AND NEURONAL ACTIVITY

Postsynaptic currents can be either excitatory (EPSCs), in which the postsynaptic cell is more likely to fire an action potential, or inhibitory (IPSCs), in which the postsynaptic cell is less likely to fire. Miniature postsynaptic currents (mEPSCs and mIPSCs) are spontaneous events recorded in the presence of the action potential blocker, tetrodotoxin. Neurons are equipped with different receptors, such as ionotropic glutamate receptors, that function as ion channels and facilitate the activity of these cells. These include *N*-methyl-D-aspartic acid (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors. NMDA receptors are permeable to calcium. Glutamate receptor 1 (GluR1)-subunit-containing AMPA receptors are permeable to calcium, sodium, and potassium, whereas GluR2-subunit-containing AMPA receptors are impermeable to calcium. Kainate receptors are permeable to sodium and potassium. These receptors facilitate the excitation of the cell. By contrast, chloride-permeable receptors responding to γ-aminobutyric acid ($GABA_A$) are inhibitory. The glutamatergic and GABAergic receptors work together to balance neuronal activity in the brain to enable cognition.

Bonnet et al. (16) showed that prolonged (>10 weeks) VAD causes decline in neurogenesis, cell survival, and differentiation in the dentate gyrus likely via RA depletion, because RA is necessary for early neuronal differentiation in the adult (66). VAD-induced decreases in the expression of RARs, neurogenesis, and neuronal differentiation lead to spatial memory impairments that can be reversed by RA supplementation (16, 25, 66).

An alternative, non-RAR-mediated route for RA action on neurogenesis may be signaling through cytoplasmic binding proteins. CRABP1 can regulate cell properties by stimulating the extracellular signal-regulated kinase 1/2 (ERK1/2) (154). RA bound to CRABP1 activates ERK1/2, which affects the cell cycle by slowing proliferation and preparing stem cells for differentiation (94). Mice lacking CRABP1 display increased proliferation of neural stem cells in the hippocampus and thus neurogenesis (94). These animals display improved learning and memory performance when tested on novel object recognition and spatial memory tasks.

The ideal balance of RA is evidently crucial for normal cognitive function, as an excess of RA can also result in impaired learning and memory. Treating mice with RA decreases cell proliferation and neurogenesis and leads to spatial memory deficits (28). RA given chronically to rats causes declarative memory impairments but in higher doses enhances the long-term retrieval of implicit/procedural memory (35). These results suggest an optimal level of RA in the brain is required to maintain normal cognitive function, and deviation from this level impairs cognition. However, circumstances may exist or arise in the normal animal in which the level is too low and increased amounts of RA will improve performance. Note that levels of RA in the brain are maintained locally and vary between areas; thus, such effects may be regional. Even relatively short distances, such as between the infrapyramidal and suprapyramidal blades of the dentate gyrus, display a RA gradient (52).

Studies of VAD have been further refined in genetically modified animals (knockout models), in which specific steps in the RA signaling pathway are blocked. For example, RARβ and RARβ/RXRγ knockout mice are viable and phenotypically similar to wild-type animals but show deficits in spatial memory tasks, and their learning does not improve during acquisition phase (23). The same RARβ and RARβ/RXRγ knockout animals also display nearly complete loss of LTP and LTD in the CA1 region of the hippocampus, even though their synapses appear structurally and functionally normal (23). RXRγ single null mutant mice exhibit a selective and total deficit in LTD, whereas their LTP is unchanged. Despite the changes in LTD, spatial memory in these animals remains intact (23). Working memory is a type of short-term memory that allows temporary storage

and manipulation of information. Spatial working memory is tested using spontaneous alternation in the Y maze, in which an animal must remember which arm of the maze was previously visited. This contrasts, for instance, with recognition working memory, which is tested by determining whether an animal recognizes a novel object that has not been previously presented to them in a novel object recognition test. The RXRγ single null and RARβ/RXRγ double null mutants show deficits in working memory tests (104, 156). Additionally, studies of the RARβ/RXRγ knockout mice showed that these receptors are important for long-term declarative (conscious) memory, which reflects cognitive flexibility (an ability to change from one learned response to another) (104).

HSP: homeostatic synaptic plasticity

Studies of knockouts have been further refined through the use of conditional knockouts. The selective ablation of RARα from layer 5 pyramidal neurons of the somatosensory cortex has revealed that this receptor is required for normal tactile sensory function (117). Mice recognize different textures by use of their whiskers. Deletion of RARα impairs whisker-dependent discrimination of texture (117). The authors of this study have also shown that RA maintains stable and mature dendritic spines, as conditional RARα knockout animals display increased elimination of them. The formation of dendritic spines is another aspect of neuroplasticity because these are the points on dendrites where the axons from other neurons make their synaptic contact (**Figure 1**). The same study also found that RARα is required for experience-dependent spine remodeling (117).

2.3. Retinoic Acid and Neuroplasticity in the Hippocampus: Homeostatic Synaptic Plasticity

Homeostatic synaptic plasticity (HSP) (see the sidebar titled Homeostatic Synaptic Plasticity) is another type of plasticity at the synapse that is dependent on RA and crucial for learning and memory. The process of strengthening or weakening the synapse to stabilize firing and maintain homeostasis is known as synaptic scaling (146).

Integral to RA's involvement in HSP is the interrelationship of RA with intracellular calcium, the concentration of which determines neuronal activity. Many studies have investigated the interaction between calcium, calcium-related and calcium-dependent proteins, and RA. For instance, rats on a VAD diet for 52 days display excessive calcium accumulation in the brain (121). Importantly, calcium also feeds back on RA. Wang et al. (152) applied a calcium channel

HOMEOSTATIC SYNAPTIC PLASTICITY

Changes to the neuronal environment are essential for learning and memory. These changes are rapid and rely on the specific adaptation of individual synapses [long-term potentiation (LTP) and long-term depression (LTD)]. Homeostatic synaptic plasticity (HSP) allows neurons to adapt to such a dynamically changing environment (54). In this form of plasticity, the strength of a neuron's synapses is finely tuned, which leads to the stabilization of neuronal networks through alterations to negative feedback loops (93, 146). Neurons are equipped with calcium-sensing mechanisms that allow them to recognize changes in activity and maintain functional stability (146). One form of this maintenance is receptor trafficking and insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamatergic receptors into the postsynaptic plasma membrane (146). HSP changes neuronal excitability, the strength of synapses, and the number of their contacts and includes spine remodeling (18, 30, 53, 117). HSP provides spatial and network-specific control of neuronal firing and finely tunes the excitation–inhibition balance, preventing overexcitation in the form of runaway LTP (74, 119).

blocker (nifedipine) or calcium chelators and saw an increase in the synthesis of RA, which could be inhibited by *N*,*N*-diethylaminobenzaldehyde, an inhibitor of RA synthesis. These experiments showed that the synthesis of RA is suppressed by intracellular calcium and stimulated when calcium concentrations are low (3, 22). A calcium-binding phosphatase relevant to the interaction between calcium and RA in neural cells, and crucial for HSP, is calcineurin. Inhibition of calcineurin supports RA production (4). Prolonged blockage of calcineurin activity in cultured hippocampal organotypic slices with cyclosporine A increases miniature excitatory PSC amplitudes and decreases miniature inhibitory PSC amplitudes. These changes happen through stimulation of RA synthesis and activation of RARα (4).

GABA: γ-aminobutyric acid

With the discovery of calcium control of RA synthesis came the integration of RA into HSP. The entire pathway of HSP can be summarized as follows: (*a*) If neuronal activity is reduced, then intracellular calcium levels fall, which stimulates synthesis of RA. (*b*) RA is then available to act on its targets and activate downstream pathways, including induction of translation of specific calcium-permeable receptors. (*c*) RA-induced increase in calcium-permeable receptors increases passage of calcium into the cell. (*d*) Rising intracellular calcium concentration halts RA synthesis and thus stabilizes neuronal activity.

RA increases the expression of calcium-permeable receptors in this system via RARα. It does not involve its typical function, regulating gene transcription, but instead involves the rapid action of RARα in the cytoplasm to regulate protein translation and thus is nongenomic. RARα is actively transported to the dendrites, where it acts as an mRNA-binding molecule, holding and blocking the translation of mRNA such as that of glutamate receptor 1 (GluR1), a crucial subunit of the AMPA receptor calcium channel. When RA binds RARα, it induces a conformational change in the receptor and the dissociation of GluR1 mRNA, making it available for translation (3, 118). Newly translated GluR1-subunit-containing AMPA receptors are inserted into the postsynaptic membrane, allowing transport of calcium into the cell, which ultimately strengthens the excitatory synapse and shuts off RA synthesis, closing the loop of HSP (**Figure 1**).

That RARα controls activity by binding to GluR1 mRNA suggests that it may act with other RNA-binding proteins. An RNA-binding functional regulator, fragile X mental retardation protein (FMRP), which is present in dendrites and the nucleus, is required for RA-induced protein synthesis of GluR1 (139). Thus, in the presence of FMRP, translation of GluR1 mRNA and insertion of AMPA receptors into the postsynaptic plasma membrane is possible. The RA-induced insertion of GluR1-containing AMPA receptors occurs exclusively in the synapses that are actively used (5). This RA-dependent increase of postsynaptic GluR1-containing AMPA receptors is mediated through a soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) mechanism (5). The SNARE proteins are fusion proteins involved in the exocytosis (membrane insertion) of AMPA receptors (70).

HSP involves not only strengthening of excitatory synapses but also weakening of inhibitory ones. RA suppresses synaptic inhibition though the removal of γ-aminobutyric acid ($GABA_A$) receptors from the synapse (128). The process also requires RARα, and FMRP is required to enhance endocytosis of these receptors. These functions of RA are crucial for the upregulation of excitatory strength and the downregulation of inhibitory strength and affect the balance of excitation and inhibition.

2.4. Retinoic Acid Regulates Cognition by Controlling the Neurotransmitter Acetylcholine and Mammalian Target of Rapamycin

RARα not only controls glutamatergic and GABAergic function but also affects the cholinergic system. Choline acetyltransferase (ChAT) is required to synthesize the neurotransmitter

acetylcholine (ACh) and is essential for memory encoding. Blocking muscarinic ACh receptors impairs memory encoding and working memory, and stimulating nicotinic ACh receptors enhances new information encoding (56). Work on murine septal cell lines showed that RA, acting on RARα, increases mRNA expression of ChAT and vesicular ACh transporter (VAChT), which is important for the storage of ACh (11).

AD: Alzheimer's disease

The action of RA on GluR1 expression also acts to modulate LTP, as part of the mechanism to regulate HSP, in a pathway that additionally involves mammalian target of rapamycin (mTOR). Conditional knockout of RARα in the CA1 region of the hippocampus resulted in overstimulated (runaway) LTP brought about by the enriched environment (59). RARα is presumed to normally act to prevent this overstimulation, first by repressing GluR1 translation and then by repressing mTOR signaling, which would otherwise also increase expression of GluR2, a second subunit of the AMPA receptor (59).

3. INVOLVEMENT OF VITAMIN A AND RETINOIC ACID IN COGNITIVE DISORDERS

Given the role of RA to support multiple essential pathways necessary for cognition in the brain, it would be expected that disruption in RA signaling would be involved in neurological diseases with clinical characteristics that include neurocognitive disorder. Neurocognitive diseases present cognitive impairment when compared with the level of cognitive function prior to disease and can include delirium, mild cognitive impairment, and dementia. The severity of the disease is assessed by impairment in one or more principal cognitive functions, including learning and memory, complex attention, perceptual-motor function, language, social cognition, and executive function (126). Disorders including autism, schizophrenia, and Alzheimer's disease (AD) disrupt cognition at different life stages; for instance, autism starts in infanthood, whereas schizophrenia is more likely to start around adolescence and AD occurs later in life. Irrespective of when these disorders start, all have been linked with changes in RA signaling.

3.1. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that usually starts before age 3 and lasts throughout life. It is characterized by stereotypical restricted and repetitive behaviors or interests and by deficits in social interaction and communication (55). A variety of conditions, including metabolic imbalance, multiple nutritional deficiencies, and increased levels of serotonin [5-hydroxytryptamine (5-HT)] in serum, are reportedly linked to autism (55). Among these conditions, vitamin and mineral deficiencies, including deficiencies in vitamins A, E, and D, calcium, and folate, are more common in children with autism than in other children (55). The developing brain is particularly sensitive to VAD because RA is required for CNS development (68, 99). As discussed in Section 2, VAD during postnatal development in rats results in cognitive impairment due to downregulation of RARα; reduced expression of the *N*-methyl-D-aspartic acid (NMDA) receptor subunit NR1, which leads to the inhibition of neuronal calcium excitability; and decreased LTP in the hippocampus (68). In addition, VAD in rats during embryonic and postnatal stages results in lower levels of histone acetylation due to the dysregulation of the cAMP response element-binding protein (CREB)-binding protein, a histone acetyltransferase regulated by RARα that contributes to impairment of spatial learning and memory in adulthood (58). A 2018 study (55) of 33 children with autism showed that administration of a single dose of a vitamin A supplement (200,000 IU) significantly increased retinol concentrations in serum, enhanced RARα and RARγ mRNA expression levels in white blood cells, decreased 5-HT levels in serum, and decreased tryptophan hydroxylase 1 expression necessary for 5-HT synthesis. The same study

found that the Childhood Autism Rating Scales (CARS) score significantly increased approximately 6 months after vitamin A was administered compared with scores from 32 healthy children in the control group (55). Considering that vitamin A levels are negatively associated with the CARS score (the lower vitamin A levels are, the more severe ASD is) (96) and that the 5-HT system plays a crucial role in sensory development, social behavior, and cognitive flexibility (55), vitamin A supplement therapy as an adjunct to other routine medications could help patients with autism with many aspects of behavior, including cognition.

DRD2: dopamine receptor D2

3.2. Schizophrenia and Schizoaffective Disorders

Schizophrenia is a severe neurodevelopmental disorder characterized by affective and psychotic positive symptoms as well as negative symptoms that eventually result in cognitive and functional impairments (see the sidebar titled The Basics of Schizophrenia). Genetic and environmental factors over the life course contribute to the development of schizophrenia (90, 108). The volume and morphology of different brain regions are affected by the disease (85, 88), and the wide range of brain regions that are affected is one reason for the general acceptance of a neurodevelopmental component to the disease (113). One of the first suggestions that RA is involved in schizophrenia was in 1995 by Goodman (49), who proposed a retinoid dysregulation hypothesis. This hypothesis linked RA signaling with schizophrenia on the basis that (*a*) the chromosomal loci of the genes associated with schizophrenia overlap with loci of the genes of RA signaling, (*b*) dysregulation of the RA signaling pathway induces congenital anomalies similar to those observed in patients with schizophrenia, and (*c*) RA regulates the transcriptional activation of genes associated with schizophrenia, including dopamine receptor D2 (*DRD2*) (50).

The strongest evidence supporting the first part of this hypothesis comes from a recent study by Reay et al. (122). They used genome-wide association studies of the Psychiatric Genomics Consortium to determine that common variants associated with schizophrenia were aggregated with retinoid genes (122). Further, from the study of the Australian Schizophrenia Research Bank, the authors found that rare variations in RARβ were linked with reduced cerebellar volume in the subtype of patients with schizophrenia with severe cognitive deficits (122). In addition, rare variations in RAREs proximal to genes regulated by RA were associated with schizophrenia (122).

THE BASICS OF SCHIZOPHRENIA

The onset of schizophrenia symptoms develops in either late adolescence or early adulthood (114). Schizophrenia is characterized by a set of core features. Positive symptoms tend to relapse and remit (psychotic symptoms associated with loss of contact with reality, e.g., visual and auditory hallucinations and delusions, and thought and perceptual disturbances) and are associated mainly with hyperactivity of the mesolimbic dopaminergic pathway, which begins at the ventral tegmental area (VTA) and ends in the ventral striatum. Negative symptoms (reduction in expression, emotions, and motivation; impairment in spontaneous speech; and social isolation and withdrawal) and cognitive impairment (a wide range of cognitive dysfunction that varies across individuals) are related to hypoactivity of the mesocortical dopaminergic pathway, which begins at the VTA and ends in the prefrontal cortex (114). Both negative and cognitive symptoms are chronic (114). A recent review suggested that striatal hyperdopaminergia, either through dysregulation of cortical dopaminergic systems or by disruption of signaling between the associative striatum and frontal cortex, results in cognitive impairments (103). Abnormalities in cortical inhibitory γ-aminobutyric acid (GABA)ergic neurons also have a key role in the pathophysiology of schizophrenia, resulting in emotional and cognitive impairments (31).

The second part of the retinoid dysregulation hypothesis arises from the neurodevelopmental hypothesis of schizophrenia and the finding that abnormal fetal development results in fragile brain function that, together with disruption to the CNS later in life, leads to schizophrenia (109). In particular, dysregulation of the striatal dopaminergic pathway is common to many of the risk factors linked to schizophrenia (109). RA has a key role in embryonic and postnatal forebrain development (84). Dysregulation in neuronal circuitry and function in the forebrain is associated with cognitive impairment in schizophrenia (84). *Aldh1a3* mutant mouse embryos show a reduction in DRD2 in the nucleus accumbens (21). They also show a decrease in the GABA-synthesizing enzyme glutamic acid decarboxylase 67 (GAD67) and a failure of the lateral ganglionic eminence progenitors to differentiate into GABAergic striatal projection neurons or of GABAergic interneurons to migrate to either the cortex or the olfactory bulb (21). Reduction in *GAD67* mRNA, along with alteration in GABAergic activity, is one of the most consistent findings in postmortem schizophrenic dorsolateral prefrontal cortex (PFC) (31). A subtype of GABAergic inhibitory interneurons that express the calcium-binding protein parvalbumin (PV) regulates excitatory and inhibitory balance as well as neuronal synchrony and has pivotal roles in higher cognitive functions (87, 157). Impairment in *GAD67* gene expression has been suggested to be limited to the PV-containing GABAergic neurons (32). Abnormalities in these neurons result in developmental brain disorders, including autism and schizophrenia (87). In this case, the impact of RA on these neurons may be via control of postnatal rather than embryonic development, because RA can regulate the development of early postnatal PV neurons in the medial PFC. The RA-degrading enzyme CYP26B1 expressed in the thalamus is essential for these inhibitory interneurons to develop normally in a regionally and temporally specific manner (87). Given the importance of RA in forebrain development, it is unsurprising that a large population-based birth cohort study showed that women in their second trimester who had less than 20 μg/dL retinol in their serum showed an increased risk of schizophrenia and schizophrenia spectrum disorders in their offspring by more than threefold (9). Thus, RA signaling has a regulatory effect on both embryonic and postnatal development of GABAergic neurons in the PFC, where abnormal function has been linked to schizoaffective and cognitive disorders.

PFC: prefrontal cortex

The last part of the retinoid dysregulation hypothesis proposes that RA regulates the transcriptional activation of genes associated with schizophrenia. A series of neurotransmitter systems, including dopamine, serotonin, GABA, ACh, and glutamate, are disrupted in schizophrenia (140, 159). Several genes and molecules associated with the normal function of these neurotransmitters are acted upon by RA signaling pathways, including dopamine, dopamine receptors, and many other neurotransmitters and metabolic enzymes (50, 85, 90). Dopamine regulates various physiological functions and behaviors, from reward-motivated systems to body movement to hormone synthesis and secretion. Dopamine exerts its function by interacting with five distinct G protein–coupled receptors. DRD2, though, is associated primarily with schizophrenia, and the only proven treatments for the disease are antagonists of DRD2; chlorpromazine and haloperidol are long-lasting DRD2 antagonists, and clozapine is a transient DRD2 antagonist (131). Of particular interest is the recent finding that the action of clozapine may be mediated in part by increasing endogenous levels of RA (123). DRD2 is extensively expressed in the CNS, pre- and postsynaptically, and particularly in the striatum, mesencephalic dopaminergic neurons, and pituitary gland (127). It regulates both dopaminergic neurons and dopamine release (127). The *DRD2* gene is directly regulated by RA via a RARE in its promoter (50, 127), while blocking dopamine signaling in adult rats by chronic haloperidol treatment results in a small but significant increase in mRNA levels of RARβ1-3 and RXRγ1, which are expressed predominantly in the striatum (86). Thus, there is a mutual regulatory system between RA receptors and DRD2 in the striatum that may impact cognitive function and schizophrenia.

Several other RA-regulated genes, including retinoic acid–induced protein 1 (*RAI1*), have been linked to schizophrenia (57). RAI1 acts as a transcription factor affecting cell growth, regulation of cell cycle, embryonic neurodevelopment, and neuronal differentiation; it directly and indirectly promotes gene transcription required for neuronal communication and circuit assembly (42). It is expressed in both the nucleus and the cytoplasm, implying roles in addition to control of transcription (42). In addition, RAI1 induces expression of brain-derived neurotrophic factor, which promotes neurogenesis and has neuroprotective actions (57). The gene *RAI1* is significantly overexpressed in the cerebral cortex of patients with schizophrenia, bipolar disorder, and major depression (57), and its levels of expression are associated with phenotype severity in patients with schizophrenia as well as their response to antipsychotic medications (90). Two single-nucleotide polymorphisms (SNPs), rs4925102 and rs9907986, in the 5′-upstream region of the *RAI1* gene are binding sites for two transcription factors, deformed epidermal autoregulatory factor 1 homolog (DEAF1), related to intellectual ability, and RARα-RXRα, respectively (42). Together, these two binding sites are responsible for 30–40% of *RAI1* mRNA expression variation in the temporal cortex and PFC (42). Furthermore, RAREs have been found in the *RAI1* promoter (45). RAI1 and RAR are coexpressed in human hippocampal neurons; RARα and RARγ are present in the nuclei and RARβ is present in both the nucleus and the cytoplasm, indicating the possibility of functional cross talk between these transcription factors (45). Because the expression of RAI1 is regulated by RA (45), the increase in RAI1 expression in patients with schizophrenia and bipolar disorder might be an indicator of dysregulated RA signaling.

Changes in the level of substrate for RA, retinol, has also been linked to schizophrenia. Two retinoid-transporting proteins, apolipoprotein E (APOE), which transports retinyl esters in chylomicrons (14), and TTR in the CSF, are downregulated in patients with schizophrenia (150), and TTR expression increased significantly after patients were treated with antipsychotic medication for 2 months (150). Such changes have the potential to alter the amount of retinol delivered to cells in the brain and hence the amount of RA generated. In addition, SNP genotyping of seven genes associated with RA function showed an association of two SNPs in *ALDH1A2* (which encodes RALDH2) in Chinese patients with schizophrenia (149), and microarray results showed *ALDH1A1* (which encodes RALDH1, a protein strongly expressed in dopaminergic neurons) was significantly reduced in patients with schizophrenia (51). This finding may suggest a connection between RA signaling and schizophrenia, although RALDH1 is also involved in synthesizing neurotransmitters, including GABA (79), and metabolizing catecholamines, including dopamine and norepinephrine (2). A postmortem study showed twofold-greater expression of RARα in the dentate gyrus of a schizophrenic brain than in that of the control (51, 124). This increase might compensate for the reduction in RA-synthesizing enzymes and an alteration to increase brain sensitivity to RA and might contribute to the upregulation of DRD2 and thus schizophrenia symptoms.

The association between RA and schizophrenia has led to the proposed use of retinoids to treat disease. Bexarotene is a third-generation RXR-selective retinoid and an FDA-approved antitumor agent used to treat advanced-stage cutaneous T cell lymphoma, lung cancer, and breast cancer (90). Besides its genomic action, it can function nongenomically to rapidly regulate phosphoinositide 3-kinase and ERK1/2, promoting neurite outgrowth (90). In two clinical studies, bexarotene was administered as an adjuvant agent (75 mg/day) together with ongoing treatment with antipsychotic medication for patients with chronic schizophrenia (91, 92). In both studies, the total Positive and Negative Syndrome Scale scores improved, while positive symptoms reduced without any improvement in negative symptoms (91, 92). Amelioration of positive symptoms might be due to the promotion of synaptic plasticity by retinoids. These results show the potential therapeutic effect of retinoids on the treatment of schizophrenia and schizoaffective disorders.

3.3. Age-Related Dementia and Cognitive Deficit

Age-related cognitive decline is a major health issue during the normal aging process. Loss of synaptic plasticity in the hippocampus is considered a key part of cognitive impairment during aging (37, 44). Both optimal macronutrients (proteins, fats, and carbohydrates) and micronutrients (vitamins and minerals) can benefit cognition during aging (32). The key role of RA signaling in memory is discussed in Section 2. Retinoid signaling in the brain declines with age, and the cognitive deficits associated with aging can be reversed by treatment with RA (37, 41). Young animals with VAD manifest cognitive deficits similar to those of aged animals, and these same animals show downregulation of RARβ and RXRβ/RXRγ mRNA in their brain and hippocampus (40). Age-related VAD in elderly subjects may be due to a change in vitamin A metabolism, leading to a decline in retinol concentration in plasma (43). In rodents, the level of RA signaling activity is proportional to the expression of target genes associated with plasticity and memory performance, including neurogranin (*NRGN*), protein kinase C substrate (*RC3*), and neuromodulin (*GAP43*) (62). Animal models of VAD exhibit brain changes associated with aging, including a decrease in hippocampal volume, neuronal dying and abnormal plasticity, loss of LTP and LTD, and a reduction in neurogenesis, all of which are reversible by administration of RA (115). In addition, a decrease in RA-mediated transcription in aged C57BL/6 mice disrupted hippocampal cellular pathways and functions necessary for long-term declarative memory and short-term/working memory, whereas administration of a vitamin A supplement had a preventive action, likely through RARβ and RXRγ as demonstrated by studies of RARβ/RXRγ knockout mice (104).

GC: glucocorticoid

RA signaling indirectly modulates plasticity, memory, and cognition through glucocorticoid (GC) pathways in the hippocampus (115), and changes in GC pathways may connect RA with cognitive loss in aging and other disorders. Both mineralocorticoid receptors and glucocorticoid receptors (GRs) are involved in this process. GC levels have an inverted-U-shape effect on cognition and plasticity and can induce age-related cognitive deficits through deficiency or chronic excess, eventually reducing hippocampal volume (115). Hyperactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis in VAD LOU/C rats has been reported, with an increase in total level of corticosterone in plasma under both basal and stress situations by which RA treatment reversed the condition to normal levels (101). By contrast, a chronic, high dose of RA administered to young rats leads to an increase in HPA axis activity and in corticosterone in plasma (20); this could be due to a derepressor effect of RARα on GRs [as explained by Hu et al. (60)]. Thus, abnormally high or low levels of RA can dysregulate the HPA axis (115). RA can induce its regulatory effect on GC levels in plasma and HPA axis activity through both the hypothalamus, regulating genes including corticotropin-releasing hormone via RARα, and the pituitary gland, inhibiting adrenocorticotropic hormone (115), and potentially through the adrenal gland (63, 101). Wistar rats with VAD showed a reduction in corticosteroid-binding globulin, a plasma GC-binding protein, which leads to higher free corticosterone in plasma in these rats. This in turn results in impaired hippocampal neurogenesis, reduced spatial memory, and increased anxiety-like behavior (15). These effects can be reversed by administration of RA (15). These VAD rats showed increases in 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1), the enzyme catalyzing regeneration of active GCs from inactive forms, in the hippocampus (15). An increase in 11β-HSD1 can result in hyperactivity of the HPA axis and a decline in hippocampal plasticity, including inhibition of neurogenesis and impairment in spatial memory (15), presumably due to higher GC levels in the hippocampus (15). In this same system, administration of RA for 1 month normalizes excess GC and memory impairment (15). This normalization of excess GC may occur because RA can negatively regulate 11β-HSD1 expression and activity, which has been shown in differentiated C2C12 myotubes (7). In summary, there is a strong relationship between GCs, RA, and cognition; RA may be important

to maintain optimal GC levels throughout the life span and particularly during aging to prevent memory and cognitive decline. Administration of RA may reduce the negative effects on memory and cognition by GC dysregulation during aging.

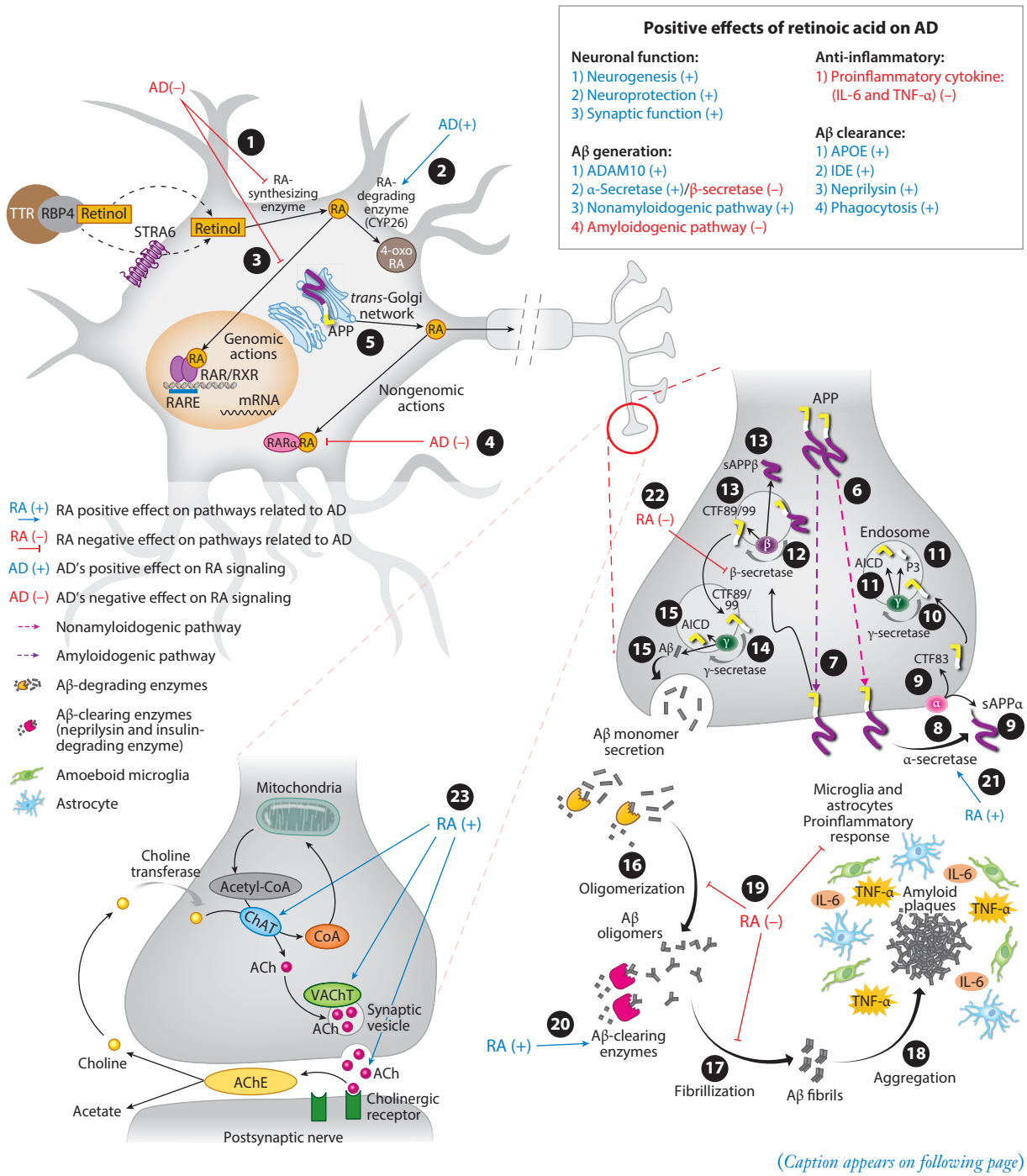
3.4. Alzheimer's Disease

AD is a neurodegenerative disease characterized by two pathological hallmarks within the brain: amyloid plaques and neurofibrillary tangles. These are caused by the formation and deposition of insoluble forms of synaptotoxic amyloid β (Aβ) peptides and neurotoxic hyperphosphorylated tau protein, respectively (47, 120, 132). These abnormal accumulations eventually lead to cognitive impairment. Most cases of AD are sporadic; however, familial AD is associated with gene mutations that favor formation of amyloid plaques and hyperphosphorylated tau.

Several studies suggest a relationship between AD pathophysiology and a reduction in RA signaling. In rats, six months of VAD downregulates RARα and reduces ChAT expression, without neuronal loss, and this precedes the deposition of Aβ seen in animals deprived of vitamin A for 1 year (26). Patients with AD on a normal diet had lower concentrations of retinol in plasma than did age-matched controls on the same diet (17). Suggestive that RA signaling itself may fall in AD is that RARs declined in five animal models of AD at early stages of disease (78). One mechanism by which RA signaling may fall in AD is through Aβ inhibition of RA synthesis (107).

Thus, if RA decline is associated with AD, then reduction in RA signaling may contribute to some of the hallmarks of the disease. Several in vitro studies indicate that genes associated with β-amyloid precursor protein (APP) processing and decreased amyloid plaque formation are regulated by RA (34, 78, 85). As a result of these studies, RA and its related compounds have been proposed as therapeutics for AD. Retinoids can decrease formation of Aβ from APP by increasing the expression and activity of the α-secretase ADAM10 (a disintegrin and metalloproteinase domain-containing protein 10) (136), the pathway shown in **Figure 2**. ADAM10 mRNA levels increase after application of RA to neuroblastoma cells (136). Another way in which retinoids may be therapeutic for AD is by preventing formation of Aβ fibrils. Vitamin A can inhibit oligomerization of Aβ40/Aβ42 in vitro (143). When treated with vitamin A, aggregated Aβ in human embryonic kidney 293 cells were less toxic than intact Aβ fibrils and oligomers (143). A variety of retinoids and β-carotene have antiamyloidogenic and fibril-destabilizing activity and could prevent Aβ fibril formation in a dose-dependent manner in vitro (112).

Several ligands of RAR and RXR have shown promise in animal models of AD and in human clinical trials (reviewed in 107). Acitretin, a RAR ligand (agonist), increased mature ADAM10, promoting α-secretase activity and thus the nonamyloidogenic pathway in neuroblastoma cells, leading to a two- to threefold increase in activity of α-secretase versus that of β-secretase (145). RA reduces β-secretase trafficking and membrane localization through activation of protein kinase C (81), thus inhibiting the amyloidogenic pathway. Administration of RA results in downregulation of β-site amyloid precursor protein–cleaving enzyme 1, acting through nuclear factor κB suppression, in the Tg2576 mouse model of AD (153). Intracerebral injection of acitretin into the APPPS1-21 mouse model of AD results in reduction of Aβ40/Aβ42 (145). In a phase 2 clinical trial, administration of oral acitretin (30 mg/day) for 4 weeks increased sAPPα levels in the CSF of patients with AD, implying an increase in nonamyloidogenic APP processing (39). Tamibarotene (Am80), a RARα/RARβ ligand (agonist) used to treat relapsed acute promyelocytic leukemia (107), reduced the level of insoluble Aβ40/Aβ42 in APP23 transgenic mice, a model of cerebral β-amyloidosis and AD (72). In addition, coadministration of Am80 with the RXR agonist HX630 to an AβPP23 mouse model of AD significantly reduced the insoluble Aβ peptide in the brain and increased the learning ability of those animals. Furthermore, this coadministration



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Reduction of RA signaling pathways through decreasing availability of retinoids in AD. (*Step 1*) Decreasing RA-synthesizing enzymes and (*Step 2*) increasing RA-degrading enzymes (e.g., CYP26) may help reduce RA bioavailability in AD, which (*Step 3*) dysregulates gene expression normally controlled by RA (107). (*Step 4*) Furthermore, AD downregulates RARα in forebrain neurons. (*Step 5*) Aβ peptide consists of 38–43 amino acids arising from proteolysis of a large transmembrane protein, APP, generated in the *trans*-Golgi network. APP is processed by α-, β-, and γ-secretases (12). Two pathways can process APP: (*Step 6*) the nonamyloidogenic APP-processing pathway and (*Step 7*) the amyloidogenic APP-processing pathway (24). In the nonamyloidogenic pathway, (*Step 8*) α-secretase cleavage of APP within the Aβ domain results in production of (*Step 9*) long soluble sAPPα and CTF83, and (*Step 10*) γ-secretase cleavage of CTF83 generates (*Step 11*) P3 and amino-terminal AICD (24). In the amyloidogenic pathway, (*Step 12*) β-secretase cleaves APP within the Aβ domain, resulting in (*Step 13*) production of sAPPβ and CTF89/99 (24). (*Step 14*) γ-Secretase cleavage of CTF89/99 generates (*Step 15*) neurotoxic Aβ40/Aβ42 peptides and the AICD (24). The ADAM family proteins regulate α-secretase activity. BACE1 is considered a major brain β-secretase (24), and the activity of γ-secretase is based on a multiprotein complex consisting of PS1 and PS2 (24, 85). The steps of Aβ formation occur in the endosomal compartment and subsequently exocytose to the extracellular region (24). Although proteases can cleave Aβ, the self-aggregation of the Aβ42 peptide leads to (*Step 16*) oligomerization and (*Step 17*) fibrillization of Aβ fragments, deposition, and (*Step 18*) amyloid plaques that eventually result in AD pathology (24). (*Step 19*) RA has antiamyloidogenic, fibril-destabilizing, and anti-inflammatory activities, and (*Step 20*) it increases Aβ clearance. Furthermore, RA promotes the nonamyloidogenic pathway and inhibits the amyloidogenic pathway through its respective (*Step 21*) positive effects on α-secretase and (*Step 22*) negative effects on β-secretase activity. (*Step 23*) Finally, RA increases ChAT and VAChT expression, which results in a rise in ACh availability in the synaptic cleft. Abbreviations: Aβ, amyloid beta; ACh, acetylcholine; AChE, acetylcholine esterase; AD, Alzheimer's disease; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; AICD, APP intracellular domain; APOE, apolipoprotein E; APP, β-amyloid precursor protein; BACE, β-site amyloid precursor protein–cleaving enzyme; ChAT, choline acetyltransferase; CoA, coenzyme A; CTF, carboxy-terminal fragment; IDE, insulin-degrading enzyme; IL, interleukin; mRNA, messenger RNA; PS, presenilin; RA, retinoic acid; RAR, retinoic acid receptor; RARE, retinoic acid response element; RBP4, retinol-binding protein 4; RXR, retinoid X receptor; sAPPα, secreted APPα; STRA6, stimulated by retinoic acid 6; TNF-α, tumor necrosis factor α; TTR, transthyretin; VAChT, vesicular ACh transporter.

elevated the mRNA level of insulin-degrading enzyme (*IDE*) and neprilysin [also known as membrane metallo-endopeptidase (*MME*)], which are Aβ-degrading enzymes, in vivo and increased activity of microglia phagocytotic activity in vitro to clear Aβ (73). Bexarotene, an RXR agonist, is also proposed as an AD therapeutic. Results suggest that it has a direct neuroprotective effect on the 5xFAD mouse model of AD by repressing inflammation and astrogliosis, preventing neuronal loss, increasing synaptic markers, and improving animal behavior (100). Bexarotene increased APOE, which can mediate Aβ clearance, and the drug reduced Aβ accumulation in the APP/PS1 mouse model of AD (27). In addition, RXR activation promotes APOE and ATP-binding cassette transporter subfamily A member 1, a major transporter required to regulate hemostasis of cellular cholesterol and phospholipid, and through various routes stimulates proteolytic Aβ degradation via extracellular IDE and microglial neprilysin (27, 67). Furthermore, bexarotene regulates microglia phagocytosis of Aβ through upregulation of the phagocytic receptor CD36 (158). Treatment with bexarotene (300 mg) for 30 days in a small clinical trial of 20 patients with AD with *APOE3* alleles showed a significant reduction in brain amyloid as well as a significant increase in triglyceride levels in serum, resulting in cardiovascular risk (29). Unfortunately, due to poor penetration of the BBB by bexarotene and to hypertriglyceridemia side effects, the outcome in the clinical trials was not satisfactory (107).

Chronic inflammation and astrocytosis are among the histopathological features of AD and are other routes by which retinoids may be therapeutic. Aβ-induced injury and plaque formation trigger inflammatory and proinflammatory responses. Aβ plaques induce phagocytic responses in microglia and they synthesize Aβ-clearing enzymes, including neprilysin and IDE, which play crucial roles in the clearance of Aβ (48). By contrast, sustained inflammatory responses caused by activated microglia are related to AD pathology; the proinflammatory cytokine tumor necrosis factor α (TNF-α) is part of this response, which results in degeneration and prevention of Aβ

clearance (48). Neurons can also express both IDE and neprilysin to clear Aβ plaques (48). RA can inhibit the production of the cytokines induced in AD inflammatory responses [e.g., interleukin 6 (IL-6) and TNF-α] via RARs expressed in cells mediating these responses (e.g., microglia and astrocytes) (136). RA treatment of the MC3T3-E1 cell line or human lung fibroblasts strongly suppresses IL-6; furthermore, it inhibits the production and expression of TNF-α and inducible nitric oxide synthase in activated microglia in rat microglia cultures (136). RA can exert its anti-inflammatory action on the CNS through glia cells: It lessens the release of neuroinflammatory factors; switches the microglia from amoeboid (active form) to ramified (resting form); and acts as a self-regulator, inducing expression of RA catabolic enzymes in microglia (136).

Changes to the cholinergic system are part of the pathophysiology of AD and are also potential targets for RA. As mentioned in Section 2.4, the presynaptic level and function of ACh, an important neurotransmitter in learning and memory, decrease in AD (25, 46), leading to the cholinergic hypothesis of AD. This hypothesis proposes that the reduction in ACh in the cerebral cortex and other parts of the brain due to the loss and degeneration of cholinergic neurons leads to cognitive impairments in patients with AD (47). Increasing ACh levels in the synaptic cleft of the AD brain is an accepted approach to slow down cognitive impairment. As discussed in Section 2.4, RA increases gene expression of the ACh-synthesizing enzymes ChAT and VAChT, which make ACh available for secretion at the nerve terminal (11). Reducing vitamin A in rats results in a fall in ACh in the hippocampus and decreases nuclear size in neurons of the CA1 region of the hippocampus, as well as reduces spatial learning (25). Scopolamine, a nonselective muscarinic antagonist, has been used as a model for inducing amnesia in young, healthy experimental animals, and drugs that reverse a scopolamine-induced cognitive deficit may be considered potential drugs for AD (47). Synthetic RAR ligands (tamibarotene, Am555S, and Tp80) and an RXR ligand (HX630) reverse the memory deficit induced by scopolamine in a passive avoidance paradigm (137). Therefore, RA can promote both production and availability of ACh at the synapse as a mechanism by which it may improve cognitive function in AD.

4. VITAMIN A AS A COGNITIVE ENHANCER

The concept that a nutritional supplement can act as a cognitive enhancer has existed for many years, sometimes with dubious providence. Whether vitamin A is such a prodigious treatment remains an open question. As discussed in Section 2.1, VAD (160) triggers disease with cognitive loss, even in the case of marginal deficiency (160), and supplementation with vitamin A is certainly beneficial in such cases. VAD may occur with normal aging (Section 3.3), although what deficiency entails is more complex than on first consideration because it is not necessarily a homogenous decline across the body. In rats, vitamin A levels in plasma fall with age but levels in local tissue can rise, perhaps in compensation (147). In association with neurodegenerative diseases such as AD, there is a local deficiency in RA signaling in the brain (Section 3.4). Disrupted vitamin A transport may be a cause of local deficiency, and the high concentrations of the retinoid-binding proteins in blood vessels of the brain and choroid plexus indicate the importance of retinoid transport across the BBB and CSF (Section 1.1). It is vital to consider the movement of vitamin A when viewing its relationship with brain function; for instance, APOE, the APOE4 polymorphism of which is linked to AD, is crucial for clearing retinyl esters from the blood (65). VAD, when assumed to mean deficiency throughout the body rather than at a specific region, is also problematic when studying its effects in humans. At least in the very elderly, retinol concentrations in plasma do not correlate with concentrations in the brain; thus, serum levels are not an effective determinant of brain concentrations (144).

Nonetheless, a few studies have found correlations between vitamin A intake and cognition. For instance, low circulating levels of retinol potentially predict increased risk of cognitive decline (61), whereas a carotenoid-rich dietary pattern may help preserve cognitive function during aging (77). Both serum and brain carotenoids correlate positively with cognitive measures (69, 97). However, a systematic review by Rutjes et al. (125) of vitamin or mineral supplements for cognitive improvement did not find evidence for the benefits of such supplements, although they suggested there was a real but small signal of effect from long-term studies of antioxidant vitamins, particularly beta-carotene. Of note, in the very elderly, concentrations of plasma carotenoids, unlike plasma retinol (see above), correlate with concentrations in the brain (144).

To conclude, vitamin A supplements do not have a major effect on cognitive improvement in the normal adult, and any small effect may be due as much to antioxidant properties as to the promotion of retinoid signaling pathways. This finding may not be surprising under normal circumstances, as systemic vitamin A is under robust homeostatic regulation and a diet high in vitamin A would just increase storage and excretion and not increase RA signaling pathways above normal. It may be hypothesized, though, that the small effects observed by some studies may represent a larger effect in a small population already depleted in vitamin A due to genetic or nutritional reasons, and that if a personalized medicine approach were tailored to individuals with VAD, the effect on cognition may be much greater.

5. CONCLUSION AND THE FUTURE

It has been realized only recently that vitamin A and RA are important for brain function and that they were not among the early discoveries of VAD research because their effects are not lethal and can require refined assays for their detection. However, these assays have revealed that vitamin A and RA are crucial for supporting neuroplasticity necessary for learning and memory as well as other cognitive processes. That the brain requires retinoids for these higher-order processes explains the high capacity of the brain to use even low levels of vitamin A through elaborate patterns of retinoid-binding proteins to capture vitamin A and its efficient capacity to convert vitamin A to RA to activate genomic and nongenomic pathways via regionally localized RARs. A common theme apparent in neurodegenerative, neurodevelopmental, and several psychiatric diseases that impact cognition is that the disrupted pathways that cause these diseases are among those necessary for RA signaling. This helps explain the decline in neuroplasticity in these disorders and may also explain changes in certain neurotransmitter pathways, including dopaminergic circuits using DRD2, in psychiatric diseases. The use of drugs targeted to RA receptors has shown promise in rebalancing some of these pathways. Further activation of these receptors may suppress the neuroinflammation evident in several of these disorders.

As a field still at a nascent stage, many questions about the roles of vitamin A and RA in the control of cognition remain unanswered, and a better understanding of these roles may provide important insights into the pathways used in particular cognitive processes. This includes vitamin A's involvement in higher-order cognitive functions and speech/language disorders evident in people with *FOXP2* mutations (89, 148). In quite a different direction, a prominent recent hypothesis linking changes in gut microbiota with numerous diseases, including AD, proposes that retinoid signaling is an intermediary (38). Finally, the hypothalamus is a hot spot in the brain for RA signaling, mediating some elements of hypothalamic control of the endocrine system and homeostasis in the body (134, 142). Tanycytes, which act as nutrient-sensing cells in the brain, are key to RA function in the hypothalamus, and this finding opens the possibility that the hypothalamus regulates vitamin A homeostasis in the body and the brain.

SUMMARY POINTS

1. Early research on vitamin A did not focus on the brain, and unlike, for instance, the eye or reproductive system, the central nervous system does not cease to function when vitamin A is deficient. This might be due in part to the high efficiency of the brain to synthesize retinoic acid (RA).
2. Vitamin A and RA are crucial, however, for neuroplasticity and aspects of brain function necessary for cognition.
3. The nongenomic action of RA to, for instance, control protein translation and activate extracellular signal-regulated kinases may be routes of signaling in the brain that are just as important as the traditional role of RA receptors to regulate transcription.
4. Neurodegenerative diseases of the brain such as Alzheimer's disease may result from a local deficiency in RA signaling due to, for instance, a fall in RAR levels.
5. Neurodegenerative, neurodevelopmental, and psychiatric diseases in which a fall in RA function leads to a decline in cognition are possible targets for treatment by RA and its analogs.

DISCLOSURE STATEMENT

P.M. is a nonexecutive director for the company Nevrargenics, a RAR-based drug development company working toward understanding, treating, and potentially reversing neurodegenerative diseases. M.U.W.-F. and A.K. are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

Support was received from a Biotechnology and Biological Sciences Research Council (BBSRC) grant (BB/P004806/1) and the National Health Service (NHS) Grampian Endowments. M.U.W.-F. is currently supported by the Intramural Research Program of the National Institutes of Health, National Institute on Aging.

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