MINIREVIEW

Retinoid-Mediated Regulation of Mood: Possible Cellular Mechanisms

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Vitamin A and its derivatives, the retinoids, have long been studied for their ability to alter central nervous system (CNS) development. Increasingly, it is recognized that sufficient levels of retinoids may also be required for adult CNS function. However, excess dietary vitamin A, due to the consumption of supplements or foods rich in vitamin A, has been reported to induce psychosis. In addition, 13-*cis*-retinoic acid (13-*cis*-RA, isotretinoin), the active ingredient in the acne treatment Accutane, has been reported to cause adverse psychiatric events, including depression and suicidal ideation. Nevertheless, epidemiological studies have reported no consistent link between Accutane use and clinical depression in humans. Using an animal model, we have recently shown that 13-*cis*-RA induces an increase in depression-related behavior. Impairments in spatial learning and memory have also been demonstrated following 13-*cis*-RA treatment in mice. This review focuses on the behavioral and possible cellular effects of retinoid deficiency or excess in the adult brain in relation to altered mood. Specifically, we discuss the effect of retinoids on depression-related behaviors and whether norepinephrinergic, dopaminergic, or serotonergic neurotransmitter systems may be impaired. In addition, we consider the evidence that adult neurogenesis, a process implicated in the pathophysiology of depression, is reduced by retinoid signaling. We suggest that 13-*cis*-RA treatment may induce depression-related behaviors by decreasing adult neurogenesis and/or altering the expression of components of serotonergic neurotransmitter system, thereby leading to impaired serotonin signaling. Exp Biol Med 233:251–258, 2008

Key words: retinoid; depression; neurogenesis; monoaminergic

Introduction

The retinoid family of compounds consists of vitamin A (retinol) and its naturally occurring and synthetic derivatives such as *all-trans*-retinoic acid (ATRA) and 13-*cis*-retinoic acid (13-*cis*-RA). A large body of work has extensively examined the role of retinoids, specifically ATRA, in central nervous system development [for review see (1)]. Retinoids are lipid soluble and easily cross the blood–brain barrier (2), so it is perhaps not surprising that over the last decade evidence has accumulated that retinoids affect adult brain function too, in particular learning and memory, locomotor activity, and depression [for review see (3, 4)]. In this review we focus on recent advances that highlight the ability of retinoids to regulate mood in the adult brain. Although we discuss the effects of other retinoids on the adult brain, this review will focus primarily on the actions of 13-*cis*-RA. 13-*Cis*-RA is the active ingredient in Accutane (Roaccutane, isotretinoin), a drug approved by the FDA in 1982 for the treatment of severe cystic or nodular acne. Since its approval, several reports concerning the ability of Accutane to induce depression and suicidal ideation have been made to the FDA and appeared in the literature, although the link between Accutane and these behaviors remains controversial [for review see (5)]. Other retinoid treatments have been linked to depressive side effects in patients as well, such as the oral retinoid

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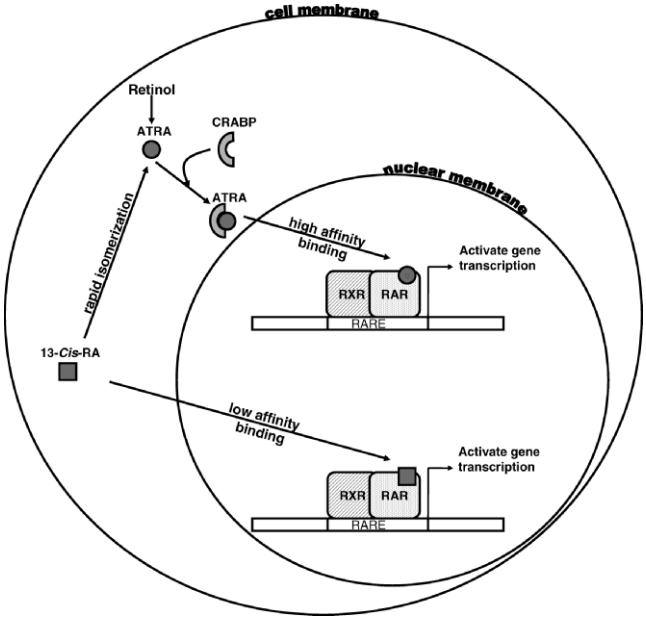

Figure 1. Retinoid mechanism of action. Inside the cell, retinol is enzymatically converted to ATRA (*all-trans*-retinoic acid). ATRA is bound to CRABPs (cellular retinoic acid binding proteins) and transported to the nucleus. In the nucleus, the RXR/RAR (retinoid X receptor/retinoic acid receptor) heterodimer binds to the RARE (retinoic acid response element) in target genes. Upon binding of ATRA to the RAR, transcription is initiated. 13-*Cis*-RA (13-*cis*-retinoic acid) either isomerizes to ATRA and then binds to the RAR to initiate gene transcription, or 13-*cis*-RA can directly bind to the RAR.

treatment for psoriasis, acitretin (6). However, the link between acitretin and depression has yet to be substantiated. After a brief explanation concerning the mechanism of action of retinoids, we will focus on recent literature concerning the role of retinoids in mediating depression-related behaviors, and discuss the possible interaction of retinoids with monoaminergic systems and adult neurogenesis, which may be dysregulated in depression.

Retinoid Mechanism of Action

Dietary retinyl esters and pre–vitamin A carotenoids are cleaved in the intestinal lumen to yield retinol, which is absorbed, re-esterified, and transported via chylomicrons to the liver. In the liver, retinyl esters are stored or processed to retinol, which circulates bound to retinol-binding protein and transthyretin (7). Circulating retinol is taken up by peripheral cells and converted to *all-trans*-retinoic acid (ATRA) via a two-step enzymatic process [for review see (3)]. ATRA, bound to cellular retinoic acid–binding proteins (CRABPs), is transported to the nucleus, where ATRA binds to nuclear retinoic acid receptors (RAR). RAR exist as heterodimers with retinoid X receptors (RXR) bound to specific regions of DNA located in the promoter regions of retinoid-responsive genes, termed retinoic acid response elements (RARE). When ATRA binds to a RAR, the RAR/RXR heterodimeric complex initiates gene transcription via the RARE (Fig. 1).

The synthetic retinoid, 13-*cis*-RA, the active ingredient in the oral acne medication, Accutane, directly regulates gene transcription in one of two ways. Firstly, 13-*cis*-RA can be isomerized to ATRA, which then binds to RAR (8). Secondly, 13-*cis*-RA itself can bind to RAR, although it does so with a much lower affinity than ATRA, and induce gene transcription via RARE (9) (Fig. 1). As described below, 13-*cis*-RA also exerts non-transcriptionally–mediated effects on cultured serotonergic cells (10).

The adult brain expresses all of the cellular machinery required for cellular retinoid trafficking and retinoid-mediated gene transcription. Specifically, cellular retinol-binding protein I expression can be found in the adult hippocampus, meninges, amygdala, and olfactory bulb (11, 12). These areas of the adult brain synthesize ATRA from retinol (12–14). CRABP-I is expressed in the hippocampus and olfactory bulb where it is thought to facilitate the degradation of ATRA to 4-oxo-retinoic acid, thereby preventing ATRA toxicity (11). RARα and β are present at high levels in the adult brain (15). RARα exhibits a widespread pattern of distribution with high levels being found in the hippocampus and cortex (15). RXR are heterodimeric binding partners not only for RAR, but for a large number of nuclear steroid hormone receptors. All RXR are expressed in the adult brain, but RXRα and β protein levels appear to be low (15) [for review see (3)].

Retinoids and Mood

Although the liver exhibits a tremendous capacity to store retinoids, in adults, chronic daily ingestion of more than 100,000 IU [33.3 times the recommended daily allowance (RDA)] of vitamin A for at least six months or ingestion of at least 100 times the RDA in a period of hours to days is considered toxic [for review see (16)]. Vitamin A toxicity is more common in children than adults, and the incidence of vitamin A toxicity may increase with the advent of dietary supplements containing high levels of retinyl esters (17). Inuit populations often consume high levels of vitamin A in the livers of seals, sharks, and predatory mammals, resulting in the phenomenon termed "pibloktoq," also known as "arctic hysteria" (18). Retinoid toxicity manifests as intense headaches, due to increased intracranial pressure resulting from excess cerebrospinal fluid, termed "pseudotumor cerebrei," dry skin and hair loss, bone, joint, and muscle pain, fatigue, and anorexia. In addition, hypervitaminosis A has been reported to induce psychosis (19, 20). Specifically, patients experiencing hypervitaminosis A exhibited depression, elevated anxiety, and irritability (18, 21). It is unknown if the toxic effects of excess dietary vitamin A are mediated via ATRA or by retinol. Although circulating retinol concentrations are maintained at 1–2 μM, ingestion of ATRA and 13-*cis*-RA can raise serum levels of these retinoids well above circulating retinol concentrations. Because of their lipophillic nature, retinoids can cross the blood–brain barrier

and affect various cellular processes both inclusive and exclusive of ATRA and RAR-mediated gene transcription (22–24).

Since approval of Accutane in 1982 to treat severe cystic acne, numerous reports concerning the ability of Accutane to induce depression and suicidal ideation have appeared throughout the medical literature [for review see (5)]. Between 1982 and 2002 the US FDA Adverse Event Reporting System received approximately 394 reports of depression and 37 suicides related to the use of Accutane (25). In some cases, depressive symptoms were reported to resolve once Accutane use was discontinued [for review see (5)]. Additionally, some cases report recurrence of symptoms upon rechallenge with 13-*cis*-RA (26). However, although these reports suggest a link between Accutane and depression, the epidemiological evidence is contradictory [e.g. (27) versus (28)]. Jick et al (29) conducted an epidemiological study in which no link was found between Accutane and major depressive disorder, although other types of depression were not examined.

Bremner et al (30) evaluated humans administered 13-*cis*-RA for acne treatment and compared them with antibiotic controls. Positron emission tomography scans taken before and after four months of treatment revealed a decrease in orbitofrontal cortex glucose metabolism following 13-*cis*-RA treatment (30). Patients who received antibiotic had no change in orbitofrontal cortex glucose metabolism before or after treatment (30). Although some patients taking 13-*cis*-RA reported headaches and subtle changes in irritability or mood, none of them were found to be clinically depressed, as assessed by the Hamilton Depression Scale (30). This study was done as a small pilot study, and, therefore, the treatment groups were not randomly assigned and the sample size was small. Additionally, patients who had a history of mental illness were excluded from the study. These factors could conceal mood-related changes that may be seen following 13-*cis*-RA treatment in a larger population.

The effect of 13-*cis*-RA on human behavior may be confounded by psychosocial variables related to adolescent stress and self-image. In an attempt to remove these variables, we developed a mouse model. We showed recently that administration of 1 mg/kg/day of 13-*cis*-RA, the same dose prescribed to human patients, to adolescent male DBA/2J mice induced depression-related behaviors in the forced swim and the tail suspension tests (31). In both of these behavioral tests, time spent immobile was increased in mice receiving 13-*cis*-RA when compared with mice administered vehicle control (31). Anxiety-related behavior in the open field and overall mobility were not affected by 13-*cis*-RA treatment (31). Each of these behavioral tests was conducted only once, and thus the potential influences of retinoids on learning, discussed below would not have confounded the behavioral results.

In contrast, Ferguson et al (32) treated adult rats with 7 or 15 mg/kg/day 13-*cis*-RA or ATRA and found no differences in depression-related behavior in the forced swim test. We speculate that the differences between this study and ours are likely a result of differences in age, species, dose, and administration route. Accutane is prescribed most frequently to human adolescents, so in our mouse model we began treatment at 4 weeks of age, which can be considered equivalent to human adolescence (33). We administered 13-*cis*-RA via intraperitoneal injection for 6 weeks and performed behavioral tests at 10 weeks of age (31). Ferguson et al (32) examined adult rats with treatment starting at 12 weeks and continuing to approximately 19 weeks of age, and 13-*cis*-RA was administered via oral gavage. It is conceivable that age may affect 13-*cis*-RA responsiveness. In addition, it is well established that different strains of mice and rats have different behavioral responses to antidepressant treatment (34–37). It seems likely that species or strain specific differences may account for the different behavioral responses to 13-*cis*-RA seen in mice [DBA/2J; O'Reilly et al (31)] and rats [Sprague-Dawley; Ferguson et al (32)]. Furthermore, dosing and route of administration could impact the outcomes of behavioral experiments. Both intraperitoneal injection and oral gavage are stressful procedures, which could confound behavioral studies. However, other methods of administration, such as implanted minipumps, are not feasible because of the light sensitivity and instability of 13-*cis*-RA.

Vitamin A deficiency may also affect mood and behavior. Transthyretin transports both thyroid hormone and vitamin A in the cerebrospinal fluid. Sousa et al (38) showed that transthyretin-null mice exhibited decreased immobility in the forced swim test and increased exploratory activity in the open field test, indicative of decreased depression and anxiety-related behaviors. Tissue levels of norepinephrine (NE), but not serotonin (5-hydroxytryptamine or 5-HT) or dopamine (DA), were increased in the limbic areas of transthyretin-null mice, when compared with wild-type mice. Although retinoid levels were not determined in the brains of these mice, lack of transthyretin may decrease brain vitamin A concentrations, resulting in behaviors opposite to those observed in response to retinoid excess.

Retinoids and Monoaminergic Systems

The monoamines, specifically the norepinephrinergic, serotonergic, and dopaminergic systems, are targets of antidepressant treatment. Tricyclic antidepressants and monoamine oxidase inhibitors elevate synaptic levels of both NE and 5-HT (39). NE has been implicated in depression based on much clinical data, for example depressed patients exhibit lower urinary levels of the NE metabolite, 3-methoxy-4-hydroxy-phenylglycol (40). In the transthyretin null mouse, retinol transport would theoretically be reduced, and thus the cellular levels of ATRA would also be decreased. Interestingly, tissue NE levels

were increased in limbic forebrain of the tranthyretin null mouse (38) suggesting that retinoids may influence norepinephrinergic transmission. However, the effect of retinoids on brain NE levels has not been directly examined, to our knowledge.

Selective serotonin reuptake inhibitors (SSRIs) target the serotonergic system and are thought to exert their therapeutic effect by increasing synaptic levels of 5-HT by blocking serotonin reuptake transporters (SERT). In our behavioral experiments, we observed an increase in immobility in mice administered 13-*cis*-RA corresponding to a decrease in swimming, but not climbing, behavior (31). In rats, antidepressants that target the serotonergic system increase swimming behavior (41). Conversely, antidepressants that target the norepinephrinergic system lead to an increase in climbing behavior (41). Although this has not been directly translated to mouse models, we hypothesize that the increase in immobility in our experiments was caused by the effect of 13-*cis*-RA on the serotonergic system. We have recently shown that serotonergic components in cultured raphe nuclei cells are altered following 13-*cis*-RA treatment (10). Specifically, chronic treatment led to increased intracellular levels of 5-HT, and elevated 5-HT1A receptor and SERT protein levels (10). Ferguson et al (42) examined the effect of 13-*cis*-RA administration on tissue monoamine levels in adult male and female rats. They found no effects of 13-*cis*-RA administration on 5-HT or its metabolite, 5-hydroxyindolacetic acid (5-HIAA), levels in hippocampal or frontal cortical brain homogenates. However, there was an apparent increase in 5-HT and 5-HIAA levels in the striatum of adult male rats administered 13-*cis*-RA (42). Additionally, mice fed a vitamin A–deficient diet for 4 weeks tended to have lower levels of 5-HT in striatal tissue homogenate (43).

The 5-HT1A receptor is a $G\alpha_{i/o}$-protein coupled receptor that is expressed both on 5-HT neurons of the dorsal raphe nucleus (somatodendritic autoreceptors) and in forebrain regions postsynaptic to 5-HT terminals. Activation of neuronal 5-HT1A receptors typically leads to inhibition of adenylyl cyclase and calcium channels or opening of potassium channels. Thus 5-HT1A autoreceptors mediate suppression of the firing activity of, and 5-HT release from, dorsal raphe 5-HT neurons (44). In forebrain projection areas, activation of postsynaptic 5-HT1A receptors in limbic and cortical regions reduces the activity of neurons of the limbic system. If the increases in 5-HT1A receptor we see *in vitro* in response to 13-*cis*-RA treatment are also manifest *in vivo*, then, in raphe neurons, 5-HT release could be altered and, at postsynaptic sites, network serotonergic signaling could be disrupted. Furthermore, the 5-HT1A receptor and the SERT act together to regulate synaptic 5-HT availability, so an increase in SERT levels could increase reuptake of 5-HT from the synaptic cleft and decrease 5-HT signaling. It may seem paradoxical that elevated levels of tissue or intracellular 5-HT would occur with retinoid treatment while we propose that synaptic availability of 5-HT would be decreased. The increased SERT expression and increased reuptake may account for elevated intracellular 5-HT levels following 13-*cis*-RA treatment (10, 42). Alternatively, increased synthesis or decreased catabolism could also account for changes in intracellular 5-HT levels, either as a direct result of 13-*cis*-RA treatment or as a compensatory mechanism for reduced release of 5-HT. Although retinoids very often affect transcription via RARE, retinoids have been shown to be able to both increase and decrease protein stability (45) and increase mRNA stability (46, 47), two examples of non-genomic effects of retinoids. We did not observe a concomitant increase in 5-HT1A receptor or SERT mRNA after a short period of 13-*cis*-RA treatment *in vitro*, indicating that 13-*cis*-RA can alter serotonergic signaling by exerting non-genomic effects, such as increased protein stability.

Finally, antidepressants that target the serotonergic or norepinephrinergic systems are thought to also affect the dopaminergic system. The mesolimbic DA system is a key element of the brain's motivational and reward system, and its dysregulation in depression may underlie symptoms of anhedonia [for reviews see (48, 49)]. Repeated treatment with antidepressants increases dopamine 2 (D2) receptor binding (50). ATRA has been shown to increase D2 receptor expression in the striatum (51, 52) and in cultured cells via activation of a functional RARE in its promoter region (53). RARβ/RXRβ, RARβ/RXRγ, and RXRβ/RXRγ double null mice have decreased expression of D2 receptor (54). This is not true for the corresponding single null mice. Additionally, transcription of tyrosine hydroxylase and dopamine β hydroxylase, the enzymes involved in DA synthesis, is decreased by ATRA in rat superior cervical ganglia neurons (55–57). However, the tyrosine hydroxylase promoter is activated by ATRA in human neuroblastoma cells (58). Monoamine oxidase B activity, which is primarily responsible for the degradation of DA to dihydroxyphenylacetic acid (DOPAC), is increased by ATRA in chick hepatocytes (59). In addition, the level of homovanillic acid, the final degradative product of DA, appeared to be elevated in the striatal tissue of male rats treated with 13-*cis*-RA (42). Consistent with this, DOPAC was decreased in the striatal tissue of vitamin A–deficient mice and DA levels also tended to be reduced in the striatal tissue of vitamin A–deficient mice (43).

Disturbed sleep and alterations in REM sleep can go alongside, or be a precursor for, depression (60). The monoamine neurotransmitters all play a role in mediating aspects of sleep behavior, and antidepressant drug treatment interferes with sleep [for reviews see (61, 62)]. Two case reports exist concerning the ability of 13-*cis*-RA to induce "sustained dreaming" during REM sleep (63). In addition, acute vitamin A toxicity has been reported to induce drowsiness and a strong desire to sleep (64). A role for retinoid signaling in sleep behavior has also been demonstrated by two recent papers. Maret et al (65) found that a polymorphism in the RARβ gene that increased receptor

expression was associated with decreased delta wave activity during slow wave sleep in mice. Kitaoka et al (43) showed that in vitamin A–deficient mice, REM sleep is increased and slow wave sleep is reduced. It is tempting to speculate that changes in sleep patterns may be mediated through changes in monoaminergic neurotransmitters, however, further studies need to be conducted to establish a causal link between vitamin A deficiency, increased REM, and lowered 5-HT and DA. Although Maret et al (65) did not examine dopaminergic function, the RARβ is highly expressed in the mesolimbic DA pathway and could contribute to altered dopaminergic function.

In summary, retinoids increase tissue levels of 5-HT and DA in the striatum, as well as their respective metabolites (42) while 13-*cis*-RA can also increase intracellular 5-HT in raphe nuclei, at least *in vitro* (10). Vitamin A deficiency tends to lower striatal levels of 5-HT and DA levels (43) and may increase NE levels in the forebrain (38). It is important to note that all of these studies examined *intracellular* neurotransmitter levels, not neurotransmitter release. Decreased synaptic levels of 5-HT caused by increases in 5-HT1A and SERT could alone confer the depressive effects of 13-*cis*-RA, but studies concerning the effects of retinoids on neurotransmitter release are required before we can draw any firm conclusions concerning the functional relevance of retinoids on neurotransmitter or receptor levels in various brain regions.

Retinoids and Neurogenesis

Decreased neurogenesis has been associated with mood disorders, including depression [for reviews see (66, 67)]. The phenomenon of adult neurogenesis, where new neurons proliferate and become functionally integrated with existing neurons, has been most widely studied in the hippocampus (68, 69). Long-term retinoid treatment *in vivo* decreases adult hippocampal neurogenesis (2). Specifically, when CD1 mice were treated with 13-*cis*-RA (1 mg/kg/day) for up to 6 weeks, a significant decrease in hippocampal neurogenesis was observed (2). Although these authors did not report any change in depression-related behaviors, they did demonstrate that 13-*cis*-RA treatment leads to impaired spatial learning and memory performance in the radial arm maze. A role for retinoids in learning and memory behaviors had previously been established using RAR knockout mice and vitamin A–deficient models [for review see (3)]. Interestingly, both RARβ or RARβ/RXRγ double null mutant mice and vitamin A deficiency are associated with deficits in spatial learning and memory (70–72). It may seem contradictory that RARβ and RARβ/RXRγ null mice have decreased spatial learning while chronic administration of 1 mg/kg/day of ATRA or 13-*cis*-RA to adolescent male CD1 mice also impairs learning and memory, but this may be a case where the dose makes the poison. Although physiological levels of retinoids and retinoid signaling pathways are required for neuronal differentiation and ultimately, learning and memory, pharmacological levels of retinoids may initiate other processes that inhibit neurogenesis. A hypothetical mechanism linking 13-*cis*-RA, 5-HT, and 5-HT1A with hippocampal neurogenesis is discussed below.

Many factors coordinate adult hippocampal neurogenesis including 5-HT, stress, steroids, and neurotrophic factors [for reviews see (73, 74)]. 5-HT itself has been implicated in the mechanisms of adult neurogenesis largely on the basis of the actions of antidepressants that elevate 5-HT levels (e.g. fluoxetine) and has been shown to promote neurogenesis (75). The actions of SSRIs in regulating adult neurogenesis may in part be mediated by 5-HT1A receptor activation (70, 71), although this remains uncertain (76). In addition, SSRIs and monoamine oxidase inhibitors can also increase brain-derived neurotrophic factor in the hippocampus, which could provide an alternative mechanism whereby 5-HT could regulate adult neurogenesis [for reviews see (73, 74)]. Interestingly, ATRA promotes the differentiation of adult-derived hippocampal stem cells to a neuronal phenotype (77, 78) and increases the expression of TrkB, a receptor for brain-derived neurotrophic factor (78). So it may be that retinoids can directly regulate adult neurogenesis by a mechanism independent of 5-HT.

Although there is a strong correlation between depression and decreased hippocampal volume (67), it is currently not known whether the decrease in hippocampal volume causes depression, or is merely a result of other signaling systems that are dysfunctional in depression. However, given the wide body of evidence linking neurogenesis to the pathology of depression and to the therapeutic actions of antidepressants, we speculate that the impaired neurogenesis observed following 13-*cis*-RA treatment may provide an additional mechanism whereby retinoids could influence depression-related behaviors. Studies have yet to be performed that show a direct causal relationship between 13-*cis*-RA administration, reduced neurogenesis, and induced depression-related behavior. Furthermore, decreased neurogenesis caused by 13-*cis*-RA treatment may be a result of changes in 5-HT signaling or 5-HT1A receptor expression, but could also occur by other signaling pathways such as a retinoid-mediated effects on brain-derived neurotrophic factor, its receptor, or some combination thereof.

Summary

The effects of both retinoid excess and deficiency on behavior, cellular metabolism, neurogenesis, and monoaminergic systems are summarized in Table 1. To date, there have been few systematic studies assessing the behavioral, cellular, and functional changes in the adult brain *in vivo* in response to retinoid treatment. It is important to note that the data in Table 1 are gleaned from a variety of *in vivo* studies in mice, rats, and humans as well as *in vitro* studies in cultured cells. Here we propose a model for how 13-*cis*-RA

Table 1. Effect of Retinoid Deficiency and Excess on Behavioral, Cellular, and Monoaminergic Systems[a]

System	Retinoid deficiency	Retinoid excess
Behavioral	↓ Depression (38) ↓ Anxiety (38) ↓ Spatial learning (71, 72)	↑ Depression (21, 31) ↑ Anxiety (18, 21) ↑ Irritability (18, 21) ↓ Spatial learning (2)
Cellular		
Energy metabolism	N/D	↓ Orbitofrontal cortical glucose metabolism (30)
Neurogenesis	N/D	↓ Hippocampal neurogenesis (2)
Monoamine systems		
Norepinephrinergic	↑ Limbic NE (38)	N/D
Serotonergic	↓ Striatal 5-HT and 5-HIAA (43)	↑ Striatal 5-HT and 5-HIAA (42) ↑ Intracellular 5-HT, 5-HT1A, and SERT (10)
Dopaminergic	↓ Striatal DA and DOPAC (43)	↑ Tyrosine hydroxylase (58) ↑ Monoamine oxidase B (59) ↑ Striatal homovanillic acid (42)

[a] N/D, not determined.

may interfere with the mature brain to induce depression-related behaviors (Fig. 2). On the basis of behavioral data in the forced swim test we hypothesize that serotonergic systems are likely to be disrupted following chronic 13-*cis*-RA treatment (31). *In vitro* we have shown that both 5-HT1A receptor and SERT levels are increased following 13-*cis*-RA treatment (10). If a similar effect is seen *in vivo*, then it is possible that increased 5-HT1A receptor expression in the raphe would reduce serotonergic neuron firing. Coupled with increased SERT expression at the synapse, these two actions of 13-*cis*-RA could work to reduce 5-HT availability at synapses. This reduction in serotonergic function could induce depression-related behaviors on its own. An alternative mechanism by which 13-*cis*-RA could induce depression would be to decrease adult hippocampal neurogenesis (2). We cannot yet say whether these mechanisms might act independently or are actually linked. Reduced serotonergic function could have an impact on adult neurogenesis, or retinoids may be able to directly regulate adult neurogenesis by an effect independent of 5-HT.

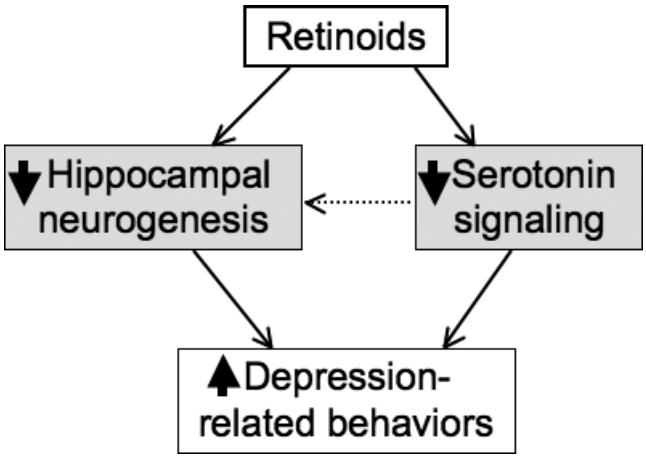

Figure 2. Proposed cellular mechanisms by which retinoids could induce an increase in depression-related behavior. Retinoids have been shown to increase depression-related behaviors in mice (31), but the mechanism by which they exert this effect is unknown. Evidence has shown that retinoids are capable of impairing adult hippocampal neurogenesis (2), an effect that is associated with increased depression-related behavior (66, 67). *In vitro*, components of serotonergic signaling are regulated by retinoids in a manner that could lead to decreased serotonergic signaling (10). This decrease in serotonergic signaling could be responsible for increased depression-related behaviors alone or could affect adult hippocampal neurogenesis.

That 13-*cis*-RA affects 5-HT signaling, thereby affecting neurogenesis to then induce depression, is a model we are currently testing, but there are a number of important caveats. While we have focused on 5-HT, we cannot exclude the possibility of altered dopaminergic function. There is ample evidence that dopaminergic pathways may be regulated by retinoid signaling, and this could contribute to changes in depression-related behaviors. In addition, retinoids may exert effects on neurotrophic factors that could contribute to altered neurogenesis, rather than an effect mediated solely by 5-HT. Furthermore, age may be an important factor in looking at mood-related behaviors in relation to retinoids. Specifically, in contrast to our observations in adolescent mice (31), in adult rats given large doses of ATRA or 13-*cis*-RA, depression-related behavior was not detectable (32). Retinoids are well-known regulators of nervous system development, shaping the neuraxis, neuronal differentiation, outgrowth, and connectivity (1). Adolescence and puberty are times of significant developmental changes in the brain, particularly in relation to motivational and emotional behaviors, that could make this age group particularly vulnerable to the effects of retinoids (33).

In conclusion, it is probably not coincidental that some patients taking Accutane exhibit clinical depression and that retinoids affect monoaminergic systems, REM sleep, and hippocampal neurogenesis. It should be noted that while

decreased orbitofrontal metabolism was seen in patients taking Accutane, this patient cohort was not found to be clinically depressed (30). In fact, only approximately 5% of patients given 13-*cis*-RA become depressed (79). This suggests that there may be a subpopulation of individuals that is susceptible to becoming depressed in response to 13-*cis*-RA treatment or increased ingestion of vitamin A. Although the direct mechanism by which retinoids affect mood remains unknown, mouse models show that 13-*cis*-RA is indeed capable of inducing depression-related behavior (31) and altering brain function (2). We are currently testing whether these effects are mediated by changes in serotonergic neurotransmission and/or effects on neuronal cell growth.

1. Maden M. Retinoid signaling in the development of the central nervous system. Nat Rev Neurosci 3:843–853, 2002.
2. Crandall J, Sakai Y, Zhang J, Koul O, Mineur Y, Crusio WE, McCaffery PJ. 13-*Cis*-retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice. Proc Natl Acad Sci U S A 101:5111–5116, 2004.
3. Lane MA, Bailey SJ. Role of retinoid signaling in the adult brain. Prog Neurobiol 72:275–293, 2005.
4. Mey J, McCaffery P. Retinoic acid signaling in the nervous system of adult vertebrates. Neuroscientist 10:409–421, 2004.
5. Hull PR, D'Arcy C. Isotretinoin use and subsequent depression and suicide. Am J Clin Dermatol 4:493–505, 2003.
6. Starling J, Koo J. Evidence based or theoretical concern? Pseudotumor cerebri and depression as acitretin side effects. J Drugs Dermatol 4: 690–696, 2005.
7. Vogel S, Gamble MV, Blaner WS. Biosynthesis, absorption, metabolism and transport of retinoids. In: Nau H, Blaner WS, Eds. Retinoids: The Biochemical and Molecular Basis of Vitamin A and Retinoid Action. Berlin Heidelberg: Springer-Verlag, pp31–95, 1999.
8. Tsukada M, Schroder M, Roos TC, Chandraratna RAS, Reichert U, Mark HF, Orfanos CE, Zouboulis CC. 13-*Cis*-retinoic acid exerts its specific activity on human sebocytes through selective intracellular isomerization to *all-trans*-retinoic acid and binding to retinoic acid receptors. J Invest Dermatol 115:321–327, 2000.
9. Idres N, Marill J, Flexor MA, Chabot GG. Activation of retinoic acid receptor-dependent transcription by *all-trans*-retinoic acid metabolites and isomers. J Biol Chem 277:31491–31498, 2002.
10. O'Reilly K, Trent S, Bailey SJ, Lane MA. 13-*Cis*-retinoic acid alters intracellular serotonin, increases 5-HT1A receptor and serotonin reuptake transporter levels *in vitro*. Exp Biol Med 232:1195–1203, 2007.
11. Zetterstrom RH, Lindqvist E, Mata de Urquiza A, Tomac A, Eriksson U, Perlmann T, Olson L. Role of retinoids in the CNS: differential expression of retinoid binding proteins and receptors and evidence for presence of retinoic acid. Eur J Neurosci 11:407–416, 1999.
12. McCaffery PJ, Drager UC. High levels of a retinoic acid-generating dehydrogenase in the meso-telencephalic dopamine system. Proc Natl Acad Sci U S A 91:7772–7776, 1994.
13. Thompson Haskell G, Maynard TM, Shatzmiller RA, Lamantia AS. Retinoic acid signaling at sites of plasticity in the mature central nervous system. J Comp Neurol 452:228–241, 2002.
14. Wagner E, Luo T, Drager UC. Retinoic acid synthesis in the postnatal mouse brain marks distinct developmental stages and functional systems. Cereb Cortex 12:1244–1253, 2002.
15. Krezel W, Kastner P, Chambon P. Differential expression of retinoid receptors in the adult mouse central nervous system. Neuroscience 89: 1291–1300, 1999.
16. Penniston K, Tanumihardjo S. The acute and chronic toxic effects of vitamin A. Am J Clin Nutr 83:191–201, 2006.
17. Lam HS, Chow CM, Poon WT, Lai CK, Chan KC, Yeung WL, Hui J, Chan AY, Ng PC. Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. Pediatrics 118:820–824, 2006.
18. Wallace A. Mental Illness, biology, and culture. In: Hsu F, Ed. Psychological Anthropology. Cambridge, MA: Shenkman, pp363–402, 1972.
19. Restak RM. Pseudotumor cerebri, psychosis, and hypervitaminosis A. J Nerv Ment Dis 155:72–75, 1972.
20. Wieland RG, Hendricks FH, Amat y Leon F, Gutierrez L, Jones JC. Hypervitaminosis A with hypercalcaemia. Lancet 1:698, 1971.
21. Muenter MD, Perry HO, Ludwig J. Chronic vitamin A intoxication in adults. Hepatic, neurologic and dermatologic complications. Am J Med 50:129–136, 1971.
22. Park EY, Dillard A, Williams EA, Wilder ET, Pepper MR, Lane MA. Retinol inhibits the growth of *all-trans*-retinoic acid-sensitive and *all-trans*-retinoic acid-resistant colon cancer cells through a retinoic acid receptor-independent mechanism. Cancer Res 65:9923–9933, 2005.
23. Park EY, Wilder ET, Lane MA. Retinol inhibits the invasion of retinoic acid-resistant colon cancer cells *in vitro* and decreases matrix metalloproteinase mRNA, protein, and activity levels. Nutr Cancer 57:66–77, 2007.
24. Dillard AC, Lane MA. Retinol decreases beta-catenin protein levels in retinoic acid-resistant colon cancer cell lines. Mol Carcinog 46:315–329, 2007.
25. Wysowski D, Pitts M, Beitz J. Depression and suicide in patients treated with isotretinoin. New Engl J Med 334:460–461, 2001.
26. Charakida A, Mouser PE, Chu AC. Safety and side effects of the acne drug, oral isotretinoin. Exp Opin Drug Saf 3:119–129, 2004.
27. Jacobs DG, Deutsch NL, Brewer M. Suicide, depression, and isotretinoin: is there a causal link? J Am Acad Dermatol 45:S168–175, 2001.
28. O'Connell KA, Wilkin JK, Pitts M. Isotretinoin (Accutane) and serious psychiatric adverse events. J Am Acad Dermatol 48:306–308, 2003.
29. Jick SS, Kremers HM, Vasilakis-Scaramozza C. Isotretinoic use and risk of depression, psychotic symptoms, suicide, and attempted suicide. Arch Dermatol 136:1231–1236, 2000.
30. Bremner JD, Fani N, Ashraf A, Votaw JR, Brummer ME, Cummins T, Vaccarino V, Goodman MM, Reed L, Siddiq S, Nemeroff CB. Functional brain imaging alterations in acne patients treated with isotretinoin. Am J Psychiatry 162:983–991, 2005.
31. O'Reilly K, Shumake J, Gonzalez-Lima F, Lane MA, Bailey SJ. Chronic administration of 13-*cis*-retinoic acid enhances depression-related behavior in mice. Neuropsychopharmacology 31:1919–1927, 2006.
32. Ferguson S, Cisneros F, Gough B, Hanig J, Berry K. Chronic oral treatment with *13-cis*-retinoic acid (isotretinoin) or *all-trans*-retinoic acid does not alter depression-like behaviors in rats. Toxicol Sci 87: 451–459, 2005.
33. Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 24:417–463, 2000.
34. Ripoll N, David DJ, Dailly E, Hascoet M, Bourin M. Antidepressant-like effects in various mice strains in the tail suspension test. Behav Brain Res 143:193–200, 2003.
35. Crowley JJ, Blendy JA, Lucki I. Strain-dependent antidepressant-like effects of citalopram in the mouse tail suspension test. Psychopharmacology (Berl) 183:257–264, 2005.
36. Lucki I, Dalvi A, Mayorga AJ. Sensitivity to the effects of pharmacologically selective antidepressants in different strains of mice. Psychopharmacology (Berl) 155:315–322, 2001.
37. Lopez-Rubalcava C, Lucki I. Strain differences in the behavioral effects

of antidepressant drugs in the rat forced swimming test. Neuropsychopharmacology 22:191–199, 2000.
38. Sousa JC, Grandela C, Fernandez-Ruiz J, de Miguel R, de Sousa L, Magalhaes AI, Saraiva MJ, Sousa N, Palha JA. Transthyretin is involved in depression-like behaviour and exploratory activity. J Neurochem 88:1052–1058, 2004.
39. Laifenfeld D, Klein E, Ben-Shachar D. Norepinephrine alters the expression of genes involved in neuronal sprouting and differentiation: relevance for major depression and antidepressant mechanisms. J Neurochem 83:1054–1064, 2002.
40. Maas JW, Fawcett JA, Dekirmenjian H. Catecholamine metabolism, depressive illness, and drug response. Arch Gen Psychiatry 26:252–262, 1972.
41. Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl) 121:66–72, 1995.
42. Ferguson S, Cisneros F, Gough B, Ali S. Four weeks of oral isotretinoin treatment causes few signs of general toxicity in male and female sprague-dawley rats. Food Chem Toxicol 43:1289–1286, 2005.
43. Kitaoka K, Hattori A, Chikahisa S, Miyamoto KI, Nakaya Y, Sei H. Vitamin A deficiency induces a decrease in EEG delta power during sleep in mice. Brain Res 1150C:121–130, 2007.
44. Blier P, Pineyro G, el Mansari M, Bergeron R, de Montigny C. Role of somatodendritic 5-HT autoreceptors in modulating 5-HT neurotransmission. Ann N Y Acad Sci:861, 1998.
45. Qin P, Haberbusch J, Soprano D, Soprano K. Retinoic acid regulates the expression of PBX1, PBX2, and PBX3 in P19 cells both transcriptionally and post-translationally. J Cell Biochem 92:147–163, 2004.
46. Motomura K, Mitsuru O, Satre M, Tsukamoto H. Destabilization of TNF-alpha mRNA by retinoic acid in hepatic macrophages: implications for alcoholic liver disease. Am J Physiol Endocrinol Metab 281: E420–E429, 2001.
47. Crowe D. Retinoic acid mediates post-transcriptional regulation of keratin 19 mRNA levels. J Cell Sci 106:183–188, 1993.
48. Naranjo CA, Tremblay LK, Busto UE. The role of the brain reward system in depression. Prog Neuropsychopharmacol Biol Psychiatry 25: 781–823, 2001.
49. Nestler EJ, Carlezon WA, Jr. The mesolimbic dopamine reward circuit in depression. Biol Psychiatry 59:1151–1159, 2006.
50. Maj J, Dziedzicka-Wasylewska M, Rogoz R, Rogoz A. Antidepressant drugs given repeatedly change the binding of the dopamine D2 receptors agonist [^{3}H]N-0437, to dopamine D2 receptors in the rat brain. Eur J Pharmacol 304:49–54, 1996.
51. Samad TA, Krezel W, Chambon P, Borrelli E. Regulation of dopaminergic pathways by retinoids: activation of the D2 receptor promoter by members of the retinoic acid receptor-retinoid X receptor family. Proc Natl Acad Sci U S A 94:14349–14354, 1997.
52. Valdenaire O, Maus-Moatti M, Vincent JD, Mallet J, Vernier P. Retinoic acid regulates the developmental expression of dopamine D2 receptor in rat striatal primary cultures. J Neurochem 71:929–936, 1998.
53. Dziedzicka-Wasylewska M, Solich J. Neuronal cell lines transfected with the dopamine D2 receptor gene promoter as a model for studying the effects of antidepressant drugs. Brain Res Mol Brain Res 128: 75–82, 2004.
54. Krezel W, Ghyselinck N, Samad TA, Dupe V, Kastner P, Borrelli E, Chambon P. Impaired locomotion and dopamine signaling in retinoid receptor mutant mice. Science 279:863–867, 1998.
55. Kobayashi M, Matsuoka I, Kurihara K. Cholinergic differentiation of cultured sympathetic neurons induced by retinoic acid. Induction of choline acetyltransferase-mRNA and suppression of tyrosine hydroxylase-mRNA levels. FEBS Letters 337:259–264, 1994.
56. Berrard S, Faucon Biguet N, Houhou L, Lamouroux A, Mallet J. Retinoic acid induces cholinergic differentiation of cultured newborn rat sympathetic neurons. J Neurosci Res 35:382–389, 1993.
57. Cervini R, Berrard S, Bejanin S, Mallet J. Regulation by CDF/LIF and retinoic acid of multiple ChAT mRNAs produced from distinct promoters. Neuroreport 5:1346–1348, 1994.
58. Jeong H, Kim MS, Kim SW, Kim KS, Seol W. Regulation of tyrosine hydroxylase gene expression by retinoic acid receptor. J Neurochem 98:386–394, 2006.
59. Nicotra A, Falasca L, Senatori O, Conti Devirgiliis L. Monoamine oxidase A and B activities in embryonic chick hepatocytes: differential regulation by retinoic acid. Cell Biochem Funct 20:87–94, 2002.
60. Seifritz E. Contribution of sleep physiology to depressive pathophysiology. Neuropsychopharmacology 25:S85–88, 2001.
61. Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. Drugs 65:927–947, 2005.
62. Argyropoulos SV, Wilson SJ. Sleep disturbances in depression and the effects of antidepressants. Int Rev Psychiatry 17:237–245, 2005.
63. Gupta MA, Gupta AK. Isotretinoin use and reports of sustained dreaming. Br J Dermatol 144:919–920, 2001.
64. Idzikowski C, Shapiro CM. ABC of sleep disorders. Non-Psychotropic drugs and sleep. BMJ 306:1118–1121, 1993.
65. Maret S, Franken P, Dauvilliers Y, Ghyselinck NB, Chambon P, Tafti M. Retinoic acid signaling affects cortical synchrony during sleep. Science 310:111–113, 2005.
66. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 93:3908–3913, 1996.
67. Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS. Hippocampal volume reduction in major depression. Am J Psychiatry 157:115–118, 2000.
68. Kempermann G, Jessberger S, Steiner B, Kronenberg G. Milestones of neuronal development in the adult hippocampus. Trend Neurosci 27: 447–452, 2004.
69. Kempermann G, Wiskott L, Gage FH. Functional significance of adult neurogenesis. Curr Opin Neurobiol 14:186–191, 2004.
70. Chaing M, Misner D, Kempermann G, Schikorski T, Giguere V, Sucov H, Gage F, Stevens C, Evans R. An essentail role for retinoid receptors RARbeta and RXRgamma in long–term potentiation and depression. Neuron 21:1353–1361, 1998.
71. Cocco S, Diaz G, Stancampiano R, Diana A, Carta M, Curreli R, Sarais L, Fadda F. Vitamin A deficiency produces spatial learning and memory impairment in rats. Neuroscience 115:475–482, 2003.
72. Etchamendy N, Enderlin V, Marighetto A, Pallet V, Higueret P, Jaffard R. Vitamin A deficiency and relational memory deficit in adult mice: relationships with changes in brain retinoid signaling. Behav Brain Res 145:37–49, 2003.
73. Castren E, Voikar V, Rantamaki T. Role of neurotrophic factors in depression. Curr Opin Pharmacol 7:18–21, 2007.
74. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59:1116–1127, 2006.
75. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110, 2000.
76. Holick KA, Lee DC, Hen R, Dulawa SC. Behavioral effects of chronic fluoxetine in BALB/cJ mice do not require adult hippocampal neurogenesis or the serotonin 1A receptor. Neuropsychopharmacology, 2007.
77. Palmer TD, Takahashi J, Gage FH. The adult rat hippocampus contains primordial neural stem cells. Mol Cell Neurosci 8:389–404, 1997.
78. Takahashi J, Palmer TD, Gage FH. Retinoic acid and neurotrophins collaborate to regulate neurogenesis in adult-derived neural stem cell cultures. J Neurobiol 38:65–81, 1999.
79. Bremner JD. Does isotretinoin cause depression and suicide? Psychopharmacol Bull 37:64–78, 2003.