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Retinoic acid and depressive disorders: Evidence and possible neurobiological mechanisms

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ABSTRACT

The retinoid family members, including vitamin A and derivatives like 13-cis-retinoic acid (ITT) and all-trans retinoic acid (ATRA), are essential for normal functioning of the developing and adult brain. When vitamin A intake is excessive, however, or after ITT treatment, increased risks have been reported for depression and suicidal ideation.

Here, we review pre-clinical and clinical evidences supporting association between retinoids and depressive disorders and discuss several possible underlying neurobiological mechanisms. Clinical evidences include case reports and studies from healthcare databases and government agency sources. Preclinical studies further confirmed that RA treatment induces hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis and typical depressive-like behaviors. Notably, the molecular components of the RA signaling are widely expressed throughout adult brain. We further discuss three most important brain systems, hippocampus, hypothalamus and orbitofrontal cortex, as major brain targets of RA. Finally, we highlight altered monoamine systems in the pathophysiology of RA-associated depression. A better understanding of the neurobiological mechanisms underlying RA-associated depression will provide new insights in its etiology and development of effective intervention strategies.

1. Introduction

The retinoid family consists of vitamin A and its metabolites 13-cis-retinoic acid (13-cis-RA or isotretinoin, ITT) and all-trans retinoic acid (ATRA). They are crucial contributors to the developing (Durst et al., 1989; Janesick et al., 2015; Maden and Holder, 1991) and adult brain (Arendt et al., 2015; Bonhomme et al., 2014; Chiang et al., 1998; Lane and Bailey, 2005; Misner et al., 2001; Nomoto et al., 2012; Stoney et al., 2016). As an important factor in the developing central nervous system (CNS), RA coordinates gene expression patterns, and regulates neuronal synaptic plasticity and neurogenesis (Hsu et al., 2019; Maden, 2002, 2007; Zhong et al., 2018). The findings that RA signaling also exists extensively in the adult brain (Fragoso et al., 2012; Krezel et al., 1999; Luo et al., 2004; McCaffery and Drager, 1994; Sakai et al., 2004; Thompson Haskell et al., 2002; Wagner et al., 2002; Zetterstrom et al., 1999, 1994) imply that also the adult brain is sensitive to RA (Bremner and McCaffery, 2008; Lane and Bailey, 2005; Mey and McCaffery, 2004).

Although previously under-recognized as a relevant neurochemical signal, several recent studies have now clearly implicated RA in the pathophysiology of depression (Abdelmaksoud et al., 2019; Bremner et al., 2012; Imoesi et al., 2019; Ludot et al., 2015; Oliveira et al., 2018; Shearer et al., 2012a; Singer et al., 2019; Suuberg, 2019). For recent reviews see (Bremner and McCaffery, 2008; Bremner et al., 2012; Kontaxakis et al., 2009; Lane and Bailey, 2005; McCaffery et al., 2006; O'Reilly et al., 2008). Excessive dietary vitamin A intake (through over-consumption of foods or supplements rich in vitamin A) has e.g. been reported to induce psychosis and to cause adverse psychiatric consequences (Bremner and McCaffery, 2008; O'Reilly et al., 2008). Moreover, associations between clinical isotretinoin (ITT) use, a synthetic retinoid that is used as an effective oral treatment for severe acne, and the onset of psychological symptoms have been abundantly reported since mid-1980s. Ever since its initial entry on the market in 1982, ITT prescription to treat severe acne has been controversial. It is the only non-psychotropic drug in the Food and Drug Administration

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(FDA) top 10 drugs that are found to be associated with depression. Symptoms may include depression, suicidal ideation and psychosis (Barak et al., 2005; Bigby and Stern, 1988; Byrne and Hnatko, 1995; Hazen et al., 1983; Ng and Schweitzer, 2003; O'Connell et al., 2003; Scheinman et al., 1990; Wysowski et al., 2001b). Moreover, recent animal studies have also confirmed that chronic administration of ITT (O'Reilly et al., 2006) or ATRA (Cai et al., 2015, 2010; Hu et al., 2013, 2016) could induce depression-related behaviors in mice and rats. Furthermore, ATRA-based chemotherapy has been long used in the clinic to treat acute promyelocytic leukemia (APL) patients (who presented with a fusion of RAR α with promyelocytic leukemia (PML)) (Hanson and Leachman, 2001; Mi et al., 2012), further raising awareness regarding the neuropsychiatric side-effects of RA therapy.

In this review, we will provide a brief overview of clinical evidence of the association of RA (mainly ITT) with depression, and will discuss recent findings concerning depression-related behavioral effects of RA (ATRA and 13-cis-RA) administration in preclinical animal studies. Several possible neurobiological mechanisms that may underlie the pathophysiology of retinoid-associated depression will also be discussed. We will mainly focus on three important brain regions: the hippocampus, given its essential role in learning and memory; the hypothalamus, as central to the hypothalamus-pituitary-adrenal (HPA) stress axis; and the orbitofrontal cortex, an important part of the prefrontal-limbic network associated with the pathophysiology of depression. Finally, we will highlight the involvement of the monoamine system in the pathophysiology of RA-associated depressive disorder.

2. Retinoid mechanism of action

Vitamin A is obtained from the diet, either from meat in the form of retinyl esters that are hydrolyzed to retinol, or from plants as beta-carotene that can be cleaved into retinaldehyde and then reduced to retinol (Bremner and McCaffery, 2008). Dietary retinyl esters and pre-vitamin A carotenoids are cleaved in the intestinal lumen to yield retinol, which is then absorbed and transported to the liver. In the liver, retinyl esters could either be directly stored or processed into retinol (Blomhoff, 1994; O'Reilly et al., 2008). Circulating retinol is converted into ATRA (chemical structure shown in Fig. 1A) (Bremner and McCaffery, 2008) via a two-step enzymatic process (including retinol dehydrogenases and retinaldehyde dehydrogenases (RALDHs)) after being taken up by peripheral cells, and bound in the plasma to retinol binding protein (RBP) (Lane and Bailey, 2005).

RA function is largely mediated via its control of gene transcription through activation of specific RA receptors. In detail, ATRA, which is bound to cellular retinoic acid-binding proteins (CRABPs), is transported into the nucleus and binds to nuclear retinoic acid receptors (RARs). These RARs then form a heterodimeric complex with retinoid X receptor (RXR). Fig. 1B (Bastien and Rochette-Egly, 2004) shows a high-resolution structure of the RAR/RXR DNA-binding domain (DBD) heterodimer. This ligand-receptor complex functions as a ligand-activated transcription factor and binds to specific regions of the DNA

located in the promoter region of retinoid-responsive genes, termed retinoic acid response elements (RARE) where it regulates gene transcription (illustrated in Fig. 1A) (di Masi et al., 2015d). On the other hand, 13-cis-RA (ITT) (chemical structure shown in Fig. 1A) (Bremner and McCaffery, 2008) can directly regulate gene transcription via two ways. First, 13-cis-RA can be isomerized to ATRA, which then binds to the RAR (Tsukada et al., 2000). Second, 13-cis-RA itself can also bind to the RAR (although with a much lower affinity compared to ATRA) and induce gene transcription via RARE (Idres et al., 2002).

Importantly, all the cellular machinery required for retinoid trafficking and retinoid-mediated gene transcription has been found to be expressed in the adult brain. Notably, there is considerable overlap between the brain areas mediating RA function and those implicated in the pathophysiology of stress or depression. For instance, expression of the cellular retinol-binding protein 1 (CRBP1) can be found in the adult hippocampus, meninges, amygdala and olfactory bulb (McCaffery and Drager, 1994; Zetterstrom et al., 1999). Consequently, in these brain areas, ATRA could be directly synthesized from retinol (McCaffery and Drager, 1994; Thompson Haskell et al., 2002; Wagner et al., 2002). RAR α and RAR β are also present at high levels in the adult brain (Krezel et al., 1999). Among them, RA primarily exerts its effects through binding to RAR α (Crandall et al., 2004; Idres et al., 2002), which exhibit a widespread distribution pattern, and high levels are found in the hippocampus, thalamus and cortex (Imoesi et al., 2019; Krezel et al., 1999). Our own studies have further demonstrated that RAR α is activated in the rat hippocampus by exogenous i.c.v. ATRA application, accompanied by HPA axis activation and depressive-like symptoms (Hu et al., 2016). By contrast, a selective antagonist of RAR α was found to ameliorate chronic stress-induced depressive symptoms (Ke et al., 2019). Together, these findings highlight a critical role for RAR α in the regulation of HPA activity (Cai et al., 2015, 2010; Hu et al., 2013), depressive-like behavior and stress-related mood disorders (Qi et al., 2015). Compared with RAR α , RAR β has a more restricted distribution pattern in the adult mouse brain, with higher expression levels found in the hypothalamus and striatum (Krezel et al., 1999). Notably, all the RXRs are further expressed in the adult brain (Lane and Bailey, 2005; O'Reilly et al., 2008).

In addition to the transcriptional control of gene expression, recent literature has emphasized an important role also for a “non-genomic”, rapid action (Aggarwal et al., 2006; Masia et al., 2007) of RA in e.g. regulating neuronal protein synthesis (Chen and Napoli, 2008) and glutamate transporters in astrocytes (Chan et al., 2012), in finetuning RA target gene expression (di Masi et al., 2015d), mediating homeostatic synaptic plasticity (Aoto et al., 2008; Maghsoodi et al., 2008), transmitter release (Liao et al., 2004), and cognitive function and cocaine-seeking behavior (Chan et al., 2012) in the adult brain. For example, chronic silencing of synaptic transmission will trigger RA synthesis, which then acts at synapses to rapidly increase synaptic strength by directly activating protein translation via a “non-genomic” mechanism (i.e. without affecting transcription) locally at the dendrites (Chen et al., 2014; Sarti et al., 2012). Such local protein synthesis could

Fig. 1. Chemical structure of all-trans retinoic acid (ATRA) and 13-cis retinoic acid (isotretinoin, or ITT) and the high-resolution structure of the RAR/RXR DNA-binding domain (DBD).

(A): Chemical structure of ATRA (up figure) and 13-cis retinoic acid (middle figure); bottom figure shows that upon binding of the RA-liganded RXR/RAR heterodimer to the RARE (retinoic acid response element) in the nucleus, transcription is initiated.

(B): Example of high-resolution structure of the RAR/RXR DNA-binding domain (DBD) heterodimer in complex with a DR1 element (mmdbId: 13,928). DBD confers sequence specific DNA recognition and contains 2 zinc-nucleated modules, two α -helices and a COOH-terminal extension CTE. The CII finger surface of RAR and the T box of RXR together constitutes the interfaces between the dimers. Reproduced, with permission, from Bastien and Rochette-Egly, 2004 (Fig. 2B).

not be blocked by transcription inhibitors, but was abolished by protein synthesis inhibitors, indicating a transcription-independent mechanism. Thus, RA acts as a critical synaptic signaling molecule, mediating activity-dependent regulation of protein synthesis. Regarding this, RA was further suggested to be a key synaptic activity sensor linking altered synaptic activity to the homeostatic synaptic plasticity (Chen et al., 2014).

Taken together, through both canonical transcriptional regulatory mechanism and more recently discovered “non-genomic” actions, RA is critical for neural patterning during development, as well as for neurogenesis and homeostatic synaptic plasticity in the adult brain.

3. Physiological roles of RA in the CNS system

3.1. RA modulates neural stem cell (NSC) proliferation and differentiation

In the developing nervous system, RA is a neuronal differentiation agent that can trigger differentiation of e.g. stem cells towards a neuronal or glial phenotype (Maden, 2002). RA can both increase the number of neurites and neuritic length. The genes regulated by RA during neuronal differentiation include transcription factors, structural proteins, enzymes, cellular receptors, neurotransmitters, neuropeptide hormones and growth factors (McCaffery et al., 2003). Consequently, RA plays an important role in the postnatal differentiation of pyramidal neurons in the developing cortex, and in the mature basal ganglia and hippocampus (Takahashi et al., 1999; Wagner et al., 2002).

In the adult hippocampus, the cytosolic protein cellular retinoic acid-binding protein 1 (CRABP1) was reported to e.g. mediate non-genomic activity of RA and to physiologically regulate the neural stem cell (NSC) pool and modulate hippocampus-dependent learning and memory (Lin et al., 2017). Specifically, CRABP1 activates ERK1/2 to suppress embryonic stem cell *in vitro* and NSC proliferation *in vivo*, whereas a knockout of CRABP1 results in enhanced NSC proliferation and increased neurogenesis, parallel to improved hippocampus-dependent learning and memory performance (Lin et al., 2017).

In the basal ganglia, RA treatment results in the differentiation of embryonic stem cells into GABAergic interneurons, establishing a role for RA signaling in the forebrain development (Chatzi et al., 2011). Specifically, RA is required for the activation of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67), that converts glutamate into inhibitory GABA in forebrain neurons. In addition, an *in vitro* study has found that RA could inhibit hypothalamic neural stem cell (NSC) proliferation in an organotypic slice culture system (Shearer et al., 2012b). Importantly, the RA synthesis enzyme RALDH1 was found to be expressed in the tanycytes that line the 3rd ventricle in the hypothalamic neurogenic-like region of the rat, which is influenced by diet and metabolic factors and also under photoperiodic control (Shearer et al., 2012b; Yoo and Blackshaw, 2018).

3.2. RA modulates hippocampal adult neurogenesis, synaptic plasticity and hippocampus-dependent memory

RA signaling has been critically implicated in hippocampal synaptic plasticity and spatial memory (Chiang et al., 1998; Misner et al., 2001; Wietrzyk et al., 2005), specifically in mediating the encoding of short-term working memory and long-term declarative memory (Mingaud et al., 2008). Notably, RA signaling is implicated in activity-dependent, long-term changes of the synaptic efficacy, which may underlie cellular mechanisms of learning and memory (Chen et al., 2014). In mice lacking RAR β or RAR γ , impaired LTP or LTD was found (Chiang et al., 1998). Also during aging, hypoactivity of retinoid signaling was found to be associated with hippocampal dysfunction and memory impairment, which were reversed by RAR activation through vitamin A supplementation or a short-term treatment with RA (Mingaud et al., 2008).

Since RA is required for normal CNS functioning, dysfunction would be predicted in the absence of RA, or under conditions of RA

insufficiency. Indeed, an earlier study by Bonnet et al. (2008) has reported that in Vitamin A deprived (VAD) animals, negative effects were reported, including both impaired adult neurogenesis and memory deficits in the Morris water maze (Bonnet et al., 2008; Etchamendy et al., 2003, 2001). These impairments could be restored by RA treatment. In addition, both LTP and LTD were reduced in Vitamin A deficient mice (Misner et al., 2001).

Similarly, another study reported that RA depletion results in deficient neuronal differentiation and decreased cell survival in the dentate gyrus of adult mice, suggesting RA is required already early in the adult hippocampal neurogenesis process (Jacobs et al., 2006). Therefore, RA is likely an essential factor in the stem cell niche of the adult hippocampal SGZ. Given that endogenous RA is necessary to regulate hippocampal neuronal birth and differentiation, prolonged RA depletion or vitamin A deprivation will result in altered RA homeostasis and thereby impair adult neurogenesis in the brains of the above Vitamin A deprived animals.

Taken together, a precise homeostatic control of Vitamin A or RA level is essential for normal brain function (McCaffery et al., 2003). An imbalance in RA levels and a disturbance of the normal pattern will result in abnormal changes in the developing or mature CNS.

4. Retinoid and mood disorder

4.1. Preclinical studies on depression-related behavioral effects of retinoic acid application

Preclinical evidence linking retinoic acid (RA) and depressive-like behaviors came from behavioral studies in mice, where daily intraperitoneal (i.p.) administration of 1 mg/kg 13-cis-RA (ITT), the dose most close to clinical use, to adolescent male DBA/2 J mice for 6 weeks, induced depression-related behavior in the forced swimming test and the tail suspension test (Masia et al., 2007; O'Reilly et al., 2006). Six weeks of ITT administration also induced depressive-like behavior in Wistar rats (Samuels et al., 2016), while a 19-day chronic ATRA administration in young adult rats of 8–10 weeks of age was found to induce depressive-like behavior, as reflected by decreased sucrose preference (Hu et al., 2013, 2016). In addition, a 6-week chronic ATRA administration in juvenile (4 weeks age) rats induces HPA axis hyperactivity, accompanied by anxiety-like behavior in the EPM and open field (Cai et al., 2015, 2010). Another recent study found that manipulating RA signaling enzymes, by selective knock down of the RA degradation enzyme Cyp26b1 and RA binding protein CRABP2 in the nucleus accumbens (NAc), also increased depression-related behavior (Song et al., 2017). However, also negative results have been reported. For example, Ferguson et al. reported that high doses (7 or 15 mg/kg/day) of ITT or ATRA did not affect depression-related behavior in the forced-swim test in adult rats (12–19 weeks age) (Ferguson et al., 2005a, 2007). Differences between these studies could involve differences in age (i.e. adolescent vs. adult age), and species (mice vs. rat), and the dose and administration routes (i.p. vs. oral gavage or i.c.v.) of the drugs.

Overall, the above studies in rodent models have provided evidence that: 1) RA can affect adult brain function and induce depression-related behavior in rodents; 2) younger animals may be more susceptible to RA application; 3) differences in sensitivity may exist (depending on testing species (mice vs. rats) and age (adolescent vs. adult)).

4.2. Clinical reports of retinoid-associated depression and psychosis

13-cis-RA (ITT) is a treatment for severe types of acne that are resistant to other treatments, including antibiotics and topical treatments. However, since its initial marketing in 1982, its prescription has been controversial. ITT has been associated with a variety of adverse psychiatric effects, including depression, psychosis, mood swings, violent behavior, suicide, etc (Erensoy et al., 2014; Strahan and Raimer, 2006).

ITT is now ranked in the top 10 of US Food and Drug Administration (FDA)'s database of drugs associated with reports of depression and suicidal attempts (Barak et al., 2005). Also, some patients with psychiatric symptoms have reported a history of present or past treatment with ITT (Ludot et al., 2015). The abundant studies that have demonstrated increased risks to develop depression, psychosis or suicidal ideation following ITT treatment (Hanna et al., 2016; Ludot et al., 2015) combined with a growing number of reported cases of depressive disorder associated with ITT use in patients with acne, has raised awareness and warnings. Below, we review the accumulated clinical evidence of associations between ITT treatment and depressive symptoms from clinical case reports, data-base studies and government reports.

4.2.1. Case reports

4.2.1.1. Individual cases. Villalobos et al. has reported a patient suffering from psychosis that was associated with ITT administration (Villalobos et al., 1989). After discontinuation of ITT, and treatment with antipsychotic medication, the symptoms improved over 1-month period (Bremner and McCaffery, 2008). Also, incidental cases were reported in which ITT administration was linked to depression (Bravard et al., 1993; Bremner and McCaffery, 2008; Duke and Guenther, 1993). The same case was reported (Byrne and Hnatko, 1995) when patients were evaluated with the Hamilton Depression Scale and indeed were found to suffer from clinically significant depressive symptoms. Together, although limited in numbers, these individual case reports support an association between ITT use and depression, suicidality and psychosis.

4.2.1.2. Group studies. A recent group study includes 9 patients who were treated for affective disorders while undergoing ITT therapy (Hanna et al., 2016). Among them, 4 were diagnosed with major depressive disorder, 3 with recurrent major depressive disorder, 1 with a mixed bipolar episode, and 1 with a rapid cycling bipolar I disorder. The average onset of mental disorders was reported approximately 2 months from first ITT use on.

Even larger sample study has also reported cases of depression in patients treated with ITT (Bruno et al., 1984; Friedman et al., 2006; Scheinman et al., 1990). Samples included 1419 subjects with acne and treated with ITT and 1102 subjects with psoriasis and not treated with ITT. Significant increase of mental health services utilization over a 5-year period was found specifically in ITT-treated patients (17.2 %) vs. psoriasis patients (12.5 %; $p = 0.0003$). There was also a significant increase in suicidal thoughts and suicide attempts ($p = 0.04$), consistent with known psychiatric side effects of ITT.

However, also some negative evidence exists that does not support an association of ITT use with psychiatric events (Chia et al., 2005; Ferahbas et al., 2004; Kontaxakis et al., 2009; Ng and Schweitzer, 2003), including a negative example of a 12-week study of ITT treatment (30 mg/day), where no significant differences were apparent in depression and anxiety scores (measured by Zung scales) relative to controls (Suarez et al., 2016).

To summarize, in the largest reported series of ITT treatment, estimates of the incidence of depression following ITT treatment range from 1% (Scheinman et al., 1990), 4% (Hull and Demkiw-Bartel, 2000) to 6% (Hazen et al., 1983) and 11 % (Bruno et al., 1984). Despite the above negative evidence, overall, most of the above studies suggest a potential relationship between ITT use and depression and consider ITT treatment a risk in this respect. Future epidemiological studies with larger numbers of patients will be necessary to clarify this.

4.2.1.3. Large data-base studies and data from public government agency reports. In addition to these smaller and case reports, studies from larger databases could potentially help improve risk assessment, e.g. of the link between ITT use and an increased risk for depression and suicide (Bremner et al., 2012). Several studies have used clinical

databases to assess the relationship between ITT and depression (Bremner and McCaffery, 2008). A United Health Care Study has found a significant increase in depression rate in ITT users (Bremner et al., 2012). Also, in a study from Quebec of 18,183 subjects who received ITT therapy between 1984 and 2003, ITT resulted in a statistically significant, 3-fold increased adjusted risk for depression; while minocycline, an antibiotic also used to treat acne, failed to do so (Azoulay et al., 2006).

However, some studies also have yielded inconsistent conclusion (Hersom et al., 2003; Jick et al., 2000). Limitations of these studies may include a lack of standardized diagnosis, lack of information about treatment details, a lack of a proper control group, and a limited sample size (Wysowski and Beitz, 2001). Future studies with a stronger study design, more adequate sample size, and more reliable measures will help provide us with a clearer answer.

Of note, reports of drug-related adverse events submitted to the government agencies such as FDA and WHO have also provided a prospective source of information regarding the potential relationship between ITT and depression and suicide (Bremner and McCaffery, 2008; Bremner et al., 2012). The FDA has reported a total of 431 adverse drug reactions (ADRs) for ITT use between 1982 and 2000 including committing suicide and hospitalized for either depression, suicidal ideation, or suicide attempts or suffering from depression without hospitalization (Wysowski et al., 2001a). One FDA report in 2002 has found 3104 cases of psychiatric adverse effects for ITT, 173 of which were suicides (McCoy, 2004). Another analysis of FDA's Med-watch database has shown that between 1989 and 2003, there were 216 reported drug-linked suicides in under 18-year olds. Of these, 72 were linked to ITT (Sharav, 2004). The Canadian Adverse Drug Reaction Monitoring Program (CADRMP) has reported between 1983–1999 of 16 psychiatric reactions with ITT, including depression, aggressive reaction, emotional lability, irritability, suicidal tendency, amnesia, aggravated depression, manic reaction and suicidal attempts (Bremner et al., 2012). Another analysis of subset of Canadian ADRs showed that ITT was the medication most commonly associated with adverse drug reactions (ADRs) (Carleton et al., 2007). Another important analysis of reports of ADR between 1982–1998 came from Roche, WHO and the United Kingdom Medicines Control Agency (MCA) (Bremner et al., 2012; Middelkoop, 1999). They found a much greater association of ITT with suicide or psychiatric adverse events than that of antibiotics for treatment of acne. In detail, 60 % adverse psychiatric events (including mood swings, depression, amnesia, anxiety and insomnia as well as suicide) associated with acne treatment were coupled with ITT use.

In summary, the above reports support a significant association of symptoms of depression, suicide and psychosis with ITT use from different countries that have made related adverse events public (Bremner and McCaffery, 2008). Therefore, it is suggested that patients treated with ITT should be fully informed of and warned about the risks of depression or suicide-related side-effects.

4.2.2. Temporal association between onset of depression and ITT exposure

The temporal association could be well used to judge the relationship between a drug and its putative adverse effects (Bremner and McCaffery, 2008; Bremner et al., 2012). The fact that the development of depression is temporally related to ITT treatment further supports its causal role in the pathophysiology of depression (Bremner et al., 2012). Most studies report that patients were on ITT treatment for several weeks before they developed depression and/or suicidal related behaviors, suggesting that the effects of ITT start with a delay but are long-term (Bremner and McCaffery, 2008). In addition, there are many reports that ITT-associated depressive symptoms resolved after drug treatment stopped, and sometimes the symptoms returned with re-introduction or re-challenge of the drug, including cases reported to the FDA (Bremner and McCaffery, 2008). The above examples highlight a link between the development of depression and ITT use, representing compelling evidence for a possible causal association. Also, the results

from studies on drug (dis)continuation imply that also the biological effects can normalize when ITT is removed (Bremner et al., 2012).

Furthermore, several studies have shown that patients with bipolar disorder (BD) may have an increased risk for clinical exacerbation of mood symptoms after treatment with ITT (Bigby and Stern, 1988; Cott and Wisner, 1999; Ludot et al., 2015). A retrospective review in 2010 has identified 10 patients treated with ITT among 300 BD patients, 9 of them had experienced exacerbation of mood symptoms, which began 4–20 weeks after initiation of ITT therapy and resolved after discontinuation (Schaffer et al., 2010).

5. Neurobiological mechanism for the pathophysiology of retinoid-associated depression

The overlap of brain areas implicated in RA functioning together with the link to stress/depression may provide a possible neurobiological framework to study the underlying pathophysiology of RA-induced depression (Bremner and McCaffery, 2008). We here focus on three important brain regions as major RA targets; the hippocampus (pivotal for learning and memory), the hypothalamus (essential to initiate the body's stress system, the hypothalamus-pituitary-adrenal (HPA) axis) and the orbitofrontal cortex (OFC/ventromedial prefrontal cortex; essential for executive functions) (illustrated in Fig. 5). Finally, we will discuss RA's effect on the monoamine system.

5.1. Retinoid and the Hippocampus

5.1.1. RA and RAR expression in the adult dentate gyrus

The hippocampus is a particular hotspot in RA signaling, with RAR-mediated transcription localized predominantly in the DG area (Goodman et al., 2012). High levels of RA signaling are found at the site of adult DG granule neurons and the neural precursor cells in their proximity (Fragoso et al., 2012; Hu et al., 2016; Zetterstrom et al., 1999), which continue to develop in adult-generated new neurons in this area. This adult neurogenesis has further been implicated in depression risk and in antidepressant action (Kempermann et al., 2018; Lucassen et al., 2010; Toda et al., 2019). Protein expression of RAR α , RAR γ , RXR α and RXR β was all found in the adult mouse and rat DG (Hu et al., 2016; Krezel et al., 1999). Together, they indicate abundant expression of the molecular components of retinoic acid signaling in the adult DG.

Endogenous RA in the hippocampus is generated by the RA synthetic enzyme RALDH2 (Stoney et al., 2016) present in the adjacent meninges, which has been shown to regulate hippocampal neurogenesis (Goodman et al., 2012; Sakai et al., 2004). The uneven pattern of RA signaling in the adult DG thus results from a differential distribution of the RA synthesizing enzyme RALDH2 and the catabolic enzyme Cyp26b1 (Goodman et al., 2012; McCaffery et al., 2006), which are predominantly expressed at the meninges adjacent to the infrapyramidal blade of the DG. Consequently, RA can reach the DG by diffusion from its bordering meninges. Such a spatial asymmetry creates a local RA concentration gradient in the hippocampal DG area, that is a greater for RA signaling in the lower infrapyramidal blade. This, in turn, can result in suppressed cell proliferation found in the DG infrapyramidal blade (Goodman et al., 2012).

5.1.2. RA and adult hippocampal neurogenesis

Adult neurogenesis is an important form of structural plasticity that occurs in the brain of adult mammals, including humans (Bergmann et al., 2015; Eriksson et al., 1998; Ernst and Frisen, 2015). Stem cells residing in the adult DG continue to divide and proliferate into adulthood. After migration into the granule cell layer (GCL) region, these progenitor cells will differentiate into fully functional new neurons. Functionally, the adult-born, new neurons have been implicated in the modulation of emotions (Revest et al., 2009; Snyder et al., 2011), and learning and memory (Christian et al., 2014). Notably, adult

neurogenesis has also been implicated in the pathophysiology of depression (Lucassen et al., 2019; Snyder et al., 2011; Toda et al., 2019) and antidepressant action (Surget et al., 2008). In detail, neurogenesis and their specific inputs and projections play an important role in the regulation of mood and hypothalamus-pituitary-adrenal (HPA)-axis (Drew et al., 2016; Hill et al., 2015; Opendak and Gould, 2011; Snyder et al., 2011). Moreover, intact neurogenesis is required for the efficacy of antidepressants (Santarelli et al., 2003).

The abundant presence of RA itself and its receptors (RARs) in the adult hippocampus strongly suggests (functions of) this brain region represents a likely target for RA. Within the hippocampus, RA-regulated transcription is localized predominantly in the DG area (Goodman et al., 2012). Also, adult neurogenesis is suppressed by RA signaling (Bremner and McCaffery, 2008; O'Reilly et al., 2008) while a study in mice has shown that daily intraperitoneal (i.p.) administration of 1 mg/kg 13-cis-RA (ITT), a dose similar to that used in patients, for 6 weeks, induced typical depression-related behaviors in the forced swim test and the tail suspension tests (O'Reilly et al., 2006).

Some more recent studies using a rat model have shown that chronic ATRA administration impaired all stages of adult hippocampal neurogenesis (i.e. cell proliferation, newborn cell survival and neurogenesis), and induced depression-related behavior (decreased sucrose intake in the sucrose preference test, reduced open arm entry frequency and altered duration in the elevated plus maze) (Hu et al., 2013, 2016). Fig. 2 shows an immunocytochemical example of impaired cell survival (BrdU; Fig. 2B), cell proliferation (PCNA; Fig. 2D) and reduced numbers of immature DCX neurons (DCX; Fig. 2F) in the adult DG of chronic ATRA-treated rats (vs. Control examples in Fig. 2A, C and E) (Hu et al., 2016). In addition, a 6-week chronic ATRA administration in juvenile rats caused hyperactivity of the HPA-axis, that was accompanied by anxiety or depressive-like behavior (Cai et al., 2015, 2010). Together, the above preclinical studies confirm that chronic administration of exogenous RA results in increased depressive-related behavior parallel to impaired adult hippocampal neurogenesis (Crandall et al., 2004; Sakai et al., 2004).

In the adult brain, RA is one of the factors that acts within the stem cell niche of the SVZ and SGZ to regulate neurogenesis (McCaffery et al., 2006). In the adult hippocampus, RA is an endogenous regulator of granular neuronal progenitors and neural stem cell proliferation (Bonnet et al., 2008; Goodman et al., 2012; Jacobs et al., 2006; Mishra et al., 2018; Schug et al., 2007). In addition, RARs have been found to be putative cell cycle regulators in developing neurons (Gallo et al., 2002; Janesick et al., 2015; Mao et al., 2011; Watanabe et al., 1999) and can modulate neuronal differentiation in stem cells (Aggarwal et al., 2006). Interestingly, the cellular retinoic acid-binding protein 1 (Crabp1) also modulates neural stem cell proliferation and neurogenesis (Lin et al., 2017). Thus, excess RA exposure may interfere with the normal endogenous signaling mechanisms and consequently suppress neurogenesis (Bremner and McCaffery, 2008; Crandall et al., 2004).

However, mood and anxiety disorders are highly heterogeneous, and no single theory can fully capture their complexity (Miller and Hen, 2015). While clearly involved, it is unlikely that ablation, or strong reduction, of neurogenesis *per se* can already induce a depressive phenotype. As such, future studies are needed to demonstrate that whether an RA-induced impairment in neurogenesis alone is already sufficient to induce depression, or whether it only represents one of several initial risk factors (Wang et al., 2017), that further depend on additional factors or stressors before depression develops (Hu et al., 2016; Lucassen et al., 2013, 2015).

5.1.3. Hippocampal volume change

Related to prolonged reductions in neurogenesis, another possible substrate via which RA may impact the hippocampus is by modulating its volume, which is often reduced in clinical depression. Indeed, ITT has been demonstrated to reduce hippocampal volume by 20 % after 3 weeks treatment in mice (McCaffery et al., 2006). However, due to their

Fig. 2. Example IHC figure showing chronic intracerebroventricular (i.c.v.) ATRA application suppresses hippocampal neurogenesis in the adult rat dentate gyrus (Reproduced, with permission, from Hu et al., 2016 Hippocampus (Figs. 2&5)).

(A): Distribution of double staining for 5-bromo-2-deoxyuridine (BrdU⁺)/glial fibrillary acidic protein (GFAP⁺) (BrdU⁺/GFAP⁺) cells in the DG of VEH rats. BrdU⁺ cells are mainly located in the subgranular zone (sgz) (arrowhead). Some of them are found in the hilar region. GFAP⁺ cells are mainly located in the hilus region and molecular layer (ml), except in the granular cell layer (GCL). They show stained processes and cytoplasm, while the cell nucleus is mostly without staining. Calibration bars show 50 μm.

(B): Distribution of double staining for BrdU⁺/GFAP⁺ cells in the DG of ATRA-treated rats. Less BrdU⁺ cells were found in the DG in the ATRA group. Arrow points to a typical GFAP⁺ cell. No significant difference was found in the number of GFAP⁺ cells between the two groups. Calibration bars show 50 μm.

(C): PCNA⁺ cells in the DG of VEH rats. They are clustered along the SGZ (arrowhead) and also in the hilus. Calibration bars show 50 μm.

(D): ATRA treatment resulted in less PCNA⁺ cells. Arrowhead points to a typical PCNA⁺ cell. Calibration bars show 50 μm.

(E): Immunoreactivity of DCX shown in the DG of VEH rats. DCX is mainly expressed in the SGZ and GCL, with cell body (arrow) located in the SGZ and dendrites extending through GCL into ML. Calibration bars show 100 μm.

(F): Immunoreactivity of DCX shown in the DG of ATRA-treated rats. Arrow points to the cell body of typical DCX⁺ cell. After RA treatment, DCX⁺ staining shows shorter dendrites with more frequently found gaps along the SGZ. Calibration bars show 100 μm.

(G): Sucrose preference percentage was significantly decreased in chronic all-trans retinoic acid (RA)-treated animals compared to vehicle (VEH)-treated animals. Data are presented as mean ± SEM (n = 6 animals per group; **p < 0.01).

(H): Similarly, significant positive correlation was found between PCNA⁺ cell number in the DG and corresponding sucrose preference percentage (n = 12; correlation coefficient $r = 0.908$, $p < 0.01$).

(I): Significant positive correlation was present between BrdU⁺ cell number in the DG and corresponding sucrose preference percentage (n = 12; correlation coefficient $r = 0.964$, $p < 0.01$).

(J): Again, significant positive correlation was found between DCX⁺ cell number in the DG and corresponding sucrose preference percentage (n = 12; correlation coefficient $r = 0.983$, $p < 0.01$).

Note: ** p < 0.01.

relatively small number, changes in adult neurogenesis alone are unlikely to account for a change in total volume of the entire hippocampus (Lucassen et al., 2013, 2015). Therefore, alternative mechanisms are likely involved, that have been proposed, e.g. due to reduced number of astrocytes (Verwer et al., 2007; Wang et al., 2017) or decreased number of mature neurons (Lucassen et al., 2006; Sapolsky, 2000) after ITT application (Bremner and McCaffery, 2008). Future studies will be required to better understand the mechanism.

5.2. Retinoid and the hypothalamus

5.2.1. RA and CRH expression in the hypothalamus

Another important brain area implicated in the pathophysiology of RA-induced depression is the hypothalamus. The hypothalamus is a key regulatory center of the brain involved in homeostatic control of many processes and it is further the central location where the HPA axis response during stress is initiated (Bremner et al., 2012). Several elements of the RA synthetic enzymes and the RARs have been identified in the hypothalamus (Meng et al., 2011; Ransom et al., 2014; Shearer et al., 2010) and it is thus possible that RA is synthesized endogenously and can thereafter function in the hypothalamus locally.

Our studies have indeed found that chronic ATRA treatment could induce HPA axis hyperactivity, anxiety and/or depressive-like behavior in adult rats (Cai et al., 2010; Hu et al., 2013). In the hypothalamus, corticotropin-releasing hormone (CRH) is produced by parvocellular neurons of the paraventricular nucleus (PVN) region that acts as the main driver of HPA activity, and CRH neuronal numbers are e.g. found to be elevated in depression (Raadsheer/Swaab et al., 1995). In the PVN, RAR α further co-localizes with CRH and as such, CRH can potentially act as a link between RA and depressive changes. Consistently, CRH expression in the PVN of the hypothalamus was markedly increased in ATRA-treated rats (Cai et al., 2015, 2010; Hu et al., 2013). High magnification of RAR α -immunoreactivity in the PVN has further been described between controls (Fig. 3E) and patients with affective disorder (Fig. 3F) (Chen et al., 2009). Furthermore, RAR α activation could upregulate CRH mRNA expression via a direct action on its promoter sequence (Chen et al., 2009). Similarly, RAR α levels in the hypothalamus were elevated in rats in the chronic unpredictable mild stress (CUMS) model of depression (Chen et al., 2009). In the human hypothalamus, RAR α is also expressed at high levels in the PVN (Meng et al., 2011) and increased CRH-RAR α double-stained neurons are found in the hypothalamic PVN of depressed patients (Chen et al., 2009). Examples of the immunocytochemical staining of CRH⁺ (red) and RAR α ⁺ (green) double-stained neurons in the PVN of a control subject vs. a patient with affective disorder, is compared in Fig. 3I and L (merged in yellow color) (Chen et al., 2009).

5.2.2. RAR α and GR correlation in the hypothalamus

Activation of the HPA axis is driven by CRH neurons in the hypothalamic PVN. Notably, the CRH promoter harbors a negative glucocorticoid response element (nGRE), and as corticosterone (CORT) concentrations rise (e.g. under stressful conditions), the GR will be occupied and then translocate to the nucleus where it can mediate transcription repression of CRH. Under physiological condition, GR-mediated negative feedback of CORT on the HPA axis functions will prevail and prevent its over-activation. Meanwhile, the hippocampus also exerts an inhibitory control over the hypothalamic PVN. Therefore, a moderate CORT level, with a regular circadian pattern, is maintained under stress-free conditions, which is considered optimal for brain function (illustrated in Fig. 4A).

In the PVN, both RAR α and GR co-localize with CRH (Chen et al., 2009). Interestingly, the number of RAR α and GR-immuno-positive cells correlated negatively in the rat hypothalamus (Hu et al., 2013). Under RA-induced depressive pathological conditions, however, an activated RAR α interferes with the formation of the GR repressing complex on the nGRE of the CRH promoter. This dampens GR capacity

to restrict CRH overexpression (illustrated in Fig. 4B). On the other hand, an activation of RAR α can also directly enhance CRH expression through binding to the RA response element (RARE) located on the CRH promoter (Chen et al., 2009). Together, when the above two parallel pathways are activated together, they converge and will induce CRH overexpression and HPA activation (shown in Fig. 4C) (Hu et al., 2013).

Together, our findings emphasize the importance of RA signaling also in the hypothalamus, and highlight that RA-mediated hypothalamic signaling pathways can be important for mediating elements from the pathophysiology of depression (Bremner et al., 2012). It has been suggested that augmented RA signaling in the hypothalamus of ITT-treated patients may mimic such alterations and thus represent one mechanism by which ITT can promote depression in these patients (Bremner et al., 2012).

5.3. Retinoid and the Orbitofrontal Cortex (OFC/ventromedial prefrontal cortex)

Another possible brain region that may mediate RA effects on depressive symptoms is the orbitofrontal cortex (OFC) (Bremner and McCaffery, 2008), part of the medial prefrontal cortex and part of the prefrontal-limbic network, and associated with the pathophysiology of depression (Bennett, 2011). Positron emission tomography (PET) scans have revealed that 4 months of ITT administration results in a decreased metabolism in the OFC in acne patients (Bremner et al., 2005). Importantly, the frontal cortex is one of few regions in the adult brain where RA is synthesized locally (Wagner et al., 2006) and OFC damage has indeed been shown to result in impairments in emotional regulation (Bechara et al., 1994; Berlin et al., 2004).

Patients with depression were further found to have a loss of glia and/or neurons in their OFC region (Rajkowska et al., 1999). Neuroimaging studies also show both structural and functional changes, like a smaller volume or changed gray matter thickness, altered glucose metabolism or blood flow, etc in the OFC in depression (Bremner et al., 2002; Drevets et al., 1997, 2008; Lacerda et al., 2004; Lai et al., 2000; Lee et al., 2003).

Another interesting brain imaging study has found that patients with headache that were part of a group of ITT-treated subjects, appear to have dampened OFC function (Bremner et al., 2012), consistent with another report showing that headache is associated with depression in ITT-treated patients (Wysowski and Swartz, 2005). This is not surprising given that the mammalian frontal cortex is one of the few brain regions where RA is synthesized (Wagner et al., 2006). Interestingly, the RA-degrading enzyme CYP26B1 is also found to regulate parvalbumin (PV)-expressing interneurons in the mouse medial PFC, and RA signaling has thus been suggested to play a crucial role in establishing connections between the thalamus and PFC (Larsen et al., 2019). Importantly, abnormal reductions in retinoid signaling were already found in the prefrontal cortex of depressed patients (Qi et al., 2015). Representative microphotographs of RAR α -immunoreactivity in the human ACC are shown in Fig. 3A, B, C and D (Qi et al., 2015). In addition, expression of RA-regulated retinoic acid-inducible or induced gene 1 (RAI-1) was found to be increased in the dorsolateral prefrontal cortex (DLPFC) of patients with schizophrenia, bipolar disorder and major depression (Haybaeck et al., 2015), suggesting that altered RA signaling may be a potential common pathogenic candidate in these neuropsychiatric symptoms.

The OFC has both input and output connections to the hippocampus and in turn, the hippocampus also modulates dopaminergic function in the medial PFC (Peleg-Raibstein et al., 2005). Thus, deficits in hippocampal function could lead to negative effects on the downstream OFC function (Jay et al., 2004; Rocher et al., 2004). Therefore, retinoid-induced dysregulation in the hippocampal-OFC circuit function could contribute to RA-associated depressive symptoms (Bremner et al., 2005; Ludot et al., 2015; Peleg-Raibstein et al., 2005). However, one important question that remains unclear is to which degree impaired OFC

Fig. 3. Example picture showing RARα-immunoreactivity in the human anterior cingulate cortex (ACC) and human hypothalamic paraventricular nucleus (PVN); as well as co-localization of RARα with corticotropin-releasing hormone (CRH) in the human hypothalamic PVN.

(A): Representative microphotograph of RARα-immunoreactivity in the human ACC (A–D reproduced, with permission, from Qi et al., 2015 Cerebral Cortex (Fig. 4)).

(B), (C) and (D): The same cell highlighted in each of the squares in Fig. 3(A) is shown in a higher magnification.

(E): High magnification of RARα-immunoreactivity in the PVN of a control patient; scale bar 20 μm; (E–F reproduced, with permission, from Chen et al., 2009 Biological Psychiatry (Fig. 1)).

(F): High magnification of RARα-immunoreactivity in the PVN of a patient with affective disorder; scale bar 20 μm.

(G): Confocal images of CRH (red) in the PVN of a control patient; scale bar 30 μm; (G–L reproduced, with permission, from Chen et al., 2009 Biological Psychiatry (Fig. 2)).

(H): Confocal images of RARα- (green) in the PVN of the same control patient; scale bar 30 μm.

(I): Co-localization images (yellow) show CRH-RARα double-stained cells in the PVN of the same control patient; scale bar 30 μm.

(J): Confocal images of CRH (red) in the PVN of a patient with affective disorder; scale bar 30 μm.

(K): Confocal images of RARα- (green) in the PVN of the patient with affective disorder; scale bar 30 μm.

(L): Co-localization images (yellow) show CRH-RARα double-stained cells in the PVN of the same patient with affective disorder; scale bar 30 μm.

function contributes to RA-induced depression; that is whether altered function in the OFC alone could lead to (symptoms of) depression, or whether it is actually due to previous alterations in the hippocampus, which in turn result in secondary changes in the downstream OFC function, that then together may contribute to depression. Studies using animal models in the future may help clarify these questions.

5.4. Retinoid and the monoamine system

The monoamine (specifically serotonergic, dopaminergic and noradrenergic) systems are important targets of antidepressant treatment. The general monoamine hypothesis proposes that depletion of one or more of these neurotransmitters is a key factor in the pathophysiology of depression (Delgado, 2000) while complex interactions between these three neurotransmitter systems may also exist. Here we will present evidence that indicates that each of these monoamine systems can act as an important brain target of RA (illustrated in Fig. 6).

5.4.1. Serotonergic system

Although each of the above three neurotransmitter systems may play an important role in the effects of RA signaling in depression, we will first discuss RA effect on the serotonergic system, which has been most often studied in association with RA and depression.

RAs can regulate the expression of the human serotonin transporter, by acting on a region that includes variable number tandem repeats (VNTR), and whose polymorphism is associated with a predisposition to affective disorders (Fiskerstrand et al., 1999). RA treatment may

thereby induce depression-related behaviors through altering impairments in serotonin signaling (O'Reilly et al., 2008). Indeed, patient serum 5-HT levels were shown to be directly regulated by vitamin A supplementation (Guo et al., 2018). Also, chronic ITT administration increased tissue 5-HT and 5-HIAA levels in the striatum of rats (Ferguson et al., 2005b) whereas vitamin A-deficient mice tended to have lower levels of 5-HT in the striatum (Kitaoka et al., 2007). ITT also altered the morphology of 5-HT neurons in cultured slices through a RXR- and RAR-dependent mechanism (Ishikawa et al., 2008). In addition, *in vitro* studies have confirmed an altered expression of serotonergic components in cultured raphe nuclei cells after ITT treatment, including increased intracellular 5-HT levels and 5-HT_{1A} receptor and serotonin reuptake transporters (SERT) protein levels (Charest et al., 1993; O'Reilly et al., 2007).

SERT are important targets of selective serotonin reuptake inhibitors (SSRIs), a main class of antidepressant drugs, that are thought to exert their therapeutic function by decreasing the reuptake and thereby increasing synaptic levels of 5-HT. Hence, increases in SERT expression could increase the reuptake of 5-HT from the synaptic cleft and dampen synaptic 5-HT signaling. 5-HT_{1A} receptor activation usually leads to the suppression of neuronal firing activity and 5-HT release from raphe neurons (Blair et al., 1998). 5-HT_{1A} receptor and SERT thus act together to regulate synaptic 5-HT availability. It has been suggested that decreased synaptic levels of 5-HT caused by increases in 5-HT_{1A} receptor and SERT alone could already account for the depressive effects of ITT (O'Reilly et al., 2008). Hence, if the above *in vitro* results of RA would also occur *in vivo*, then 5-HT release and the synaptic serotonergic signaling network in raphe neurons would be

Fig. 4. Example scheme showing two parallel pathways mediating RA upregulation of the corticotropin-releasing hormone (CRH) gene expression.

(A): Under physiological condition, corticosterone (CORT) level was kept at a moderate level: on the one hand, GR mediates negative feedback of CORT on the hypothalamus-pituitary-adrenal (HPA) axis to prevent HPA over-activation; on the other hand, hippocampus exerts an inhibitory influence on the hypothalamic PVN. Together, a balanced CORT level is guaranteed.

(B): Under RA-induced depressive pathological condition, a state of hyper-cortisol develops, due to: 1) a dampened hippocampal inhibitory influence on the hypothalamus; 2) a damaged GR-mediated HPA negative feedback. Together, these will result in a hyper CORT level (+ +).

(C): Example scheme showing two parallel pathways mediating RA-induced CRH overexpression through: 1) a direct transcriptional upregulation of CRH expression mediated by the RARα/RXR heterodimers bound to the RARE sequence located in the CRH promoter; and 2) a dis-inhibition process, that is suppression of the GR-mediated CRH transcriptional repression (by the GR homodimers bound to the RARE sequence located in the CRH promoter) (Reproduced, with permission, from Hu et al., 2013 *Translational Psychiatry*).

Fig. 5. RA interferes with the three brain regions, including hippocampus, hypothalamus and orbitofrontal cortex, as the major brain target to induce depressive disorders.

Impaired hippocampal neurogenesis, coupled with increased corticotropin-releasing hormone (CRH) expression in the hypothalamus, as well as impaired function of orbitofrontal cortex (OFC), will all together contribute to RA-induced depressive disorder.

altered and possibly disrupted, which could explain at least some of its depressive behavior inducing effects.

5.4.2. Dopaminergic system

While the impact of RA on the 5-HT system has been emphasized before, the involvement of altered dopaminergic or norepinephrinergic systems in the pathophysiology of RA-associated depression cannot be ignored. Considerable evidence shows that dopaminergic (Berrard et al., 1993; Cervini et al., 1994; Dziedzicka-Wasylewska and Solich, 2004; Ferguson et al., 2005b; Kitaoka et al., 2007; Kobayashi et al., 1994b; Nicotra et al., 2002; Samad et al., 1997; Valdenaire et al., 1998; Wolf, 1998) and norepinephrinergic (Matsuoka et al., 1997; O'Reilly et al., 2008; Schulpis et al., 1999) pathways are indeed influenced by RA signaling.

The mesolimbic DA system is a critical element of our motivational and reward system, and DA dysregulation may e.g. underlie the anhedonia common in depression (Naranjo et al., 2001; Nestler and Carlezon, 2006). Notably, abnormally low DA signaling has been implicated in clinical depressive disorder (Millan, 2006; Nestler and Carlezon, 2006). In particular, dopamine D2 receptor (D2R) plays an

Fig. 6. RA disrupts the monoamine system to induce depressive disorders.

The monoamine system contains serotonergic, dopaminergic and norepinephrine systems. Evidence has shown that retinoids are capable of impairing each of the serotonin system, dopamine system and the norepinephrine system. Reduction in the serotonergic function could induce depression-related behaviors (O'Reilly et al., 2008). Abnormal low DA signaling has been implicated in the clinical depressive symptoms (Millan, 2006; Nestler and Carlezon, 2006). RA could decrease NE concentration through induction of the NE transporter (Matsuoka et al., 1997). Among these three monoamine neurotransmitter systems, knowledge of the effects of RA on the NE system remains relatively limited and awaits future study.

important role in the regulation of affective behaviors.

Interestingly, high levels of retinoic acid-generating retinaldehyde dehydrogenase (RALDH) are found in the mouse meso-telencephalic dopamine system, that form a RA-generating projection from the ventral tegmentum to the corpus striatum and shell of the nucleus accumbens (NAc) (McCaffery and Drager, 1994). Importantly, RA can transcriptionally regulate D2R expression through the functional RARE in its promoter (Dziedzicka-Wasylewska and Solich, 2004). ATRA has further been shown to increase the expression of D2R in striatal tissue (Samad et al., 1997; Valdenaire et al., 1998) and cultured cells (Dziedzicka-Wasylewska and Solich, 2004). In addition, D2R in the prefrontal cortex was also a target for RA (Vincent et al., 1995) and 9-cis-RA could increase the expression of D2R in vitro (Bondioni et al., 2008; Valdenaire et al., 1998). Of note, RXR-dependent changes in the expression of D2R in the NAc have been found to underlie depressive-like behaviors (Krezel et al., 1998; Krzyzosiak et al., 2010; Samad et al., 1997). Moreover, ATRA has been shown to increase monoamine oxidase B (responsible for DA degradation) activity (Nicotra et al., 2002) and decrease transcription of tyrosine hydroxylase and dopamine β hydroxylase (DA synthesis enzymes) (Berrard et al., 1993; Cervini et al., 1994; Kobayashi et al., 1994b). Finally, expression of dopamine transporter (DAT) (Hohmann et al., 2011) and dopamine D1 receptor (Wang and Liu, 2005) was also increased by ATRA application in vitro. All of the above regulations likely contribute to a down-regulation of DA level observed in the brain of MDD patients. Together, the above data provide evidence that changes in the expression of D2R and D1R, as well as in the DA transporter, DA synthesis and degradation enzymes, may all contribute to a dampened DA system and possibly underlie the pathophysiology of RA-associated depressive behaviors.

5.4.3. Norepinephrine system

Norepinephrine (NE) is another important monoamine system implicated in the etiology of depression. Depressed patients often exhibit lower urinary levels of the NE metabolite MHPG (Maas et al., 1972) while lower levels of NE metabolites were also found in the CSF of depressed bipolar patients (Muscettola et al., 1984; Schatzberg et al., 1989). Conversely, synaptic NE levels were elevated by tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (Laifeld et al.,

2002). Among these three monoamine neurotransmitter systems, knowledge of the effects of RA on the NE system remains rather limited. In vitro RA treatment could reduce noradrenaline levels in cell lines (Handler et al., 2000). RA could decrease NE concentration in a short term through induction of the NE transporter (Matsuoka et al., 1997), which terminates the noradrenergic neurotransmission through reuptake of NE (Bremner and McCaffery, 2008). On the contrary, vitamin A deficiency could increase NE levels in the forebrain (Sousa et al., 2004). Future studies are necessary to fully elucidate these mechanisms.

Together, the above changes in the structure and function of the hippocampus, hypothalamus, orbitofrontal cortex, as well as distinct alterations in the monoamine systems could all contribute to RA-associated depressive symptoms (Box 1 and 2). Importantly, we also noted a potential interplay between impaired adult hippocampal neurogenesis and decreases in serotonergic signaling, which may actually be linked together rather than acting independently. For example, 5-HT has been implicated in the process of adult neurogenesis (Chan et al., 2012; Imoesi et al., 2019; Mahar et al., 2014; Samuels et al., 2016; Song et al., 2017), via regulating brain-derived neurotrophic factor signaling in the hippocampus (Castren et al., 2007; Duman and Monteggia, 2006; O'Reilly et al., 2008). Therefore, reductions in serotonergic function mediated at least in part by RA (metabolites) could be responsible for depression-related behavior, either independently or together through e.g. alterations in adult neurogenesis. Further studies concerning the RA effects on monoaminergic neurotransmitter release are required to better understand the exact effects of RA on the signaling cascades of each monoamine class would allow to delineate the exact role each monoamine system plays in the functional effects of RA on depression, as well as their potential interactions.

6. Summary

In this review, we have outlined evidence for an association of excess vitamin A intake or ITT treatment and depression, including clinical evidence as well as preclinical evidence from animal models. Together, they support the notion that elevated retinoid levels form a significant risk factor for depressive symptoms and mood disorders. We also highlight possible cellular mechanisms by which RA could act and induce depressive-related behavior. In particular, alterations in the monoamine systems appear a key target involved in the pathophysiology of RA-associated depression.

However, at present, there is no single well-accepted neuropharmacological mechanism that alone could account for the RA-associated psychiatric symptomatology, given that RA has a variety of effects on the various neurochemical systems in the brain. RA may influence the monoamine system, interfere with hippocampal neurogenesis, and with hypothalamic and prefrontal cortex functions. Moreover, complex interrelations may exist between these actions. More in-depth research is needed to ascertain what exact role each of these actions play in the etiology of depression (Hull and D'Arcy, 2003). Furthermore, we only focused on the hippocampus, hypothalamus and the orbitofrontal cortex as the main target brain regions of RA. However, retinoid receptors are widely distributed in the brain. Dysregulation in the function, structure or signaling also in these other brain areas could together contribute to depressive symptoms. Future studies are needed to fully understand the pathophysiology of RA-associated depression, and to develop possible safe and effective intervention strategies.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Box 1**The Monoamine system and the pathophysiology of major depression****1. Serotonin system:**

5-HT: Reduced 5-HT levels have been implicated in major depression disorder (MDD). Many antidepressants e.g. enhance overall 5-HT neurotransmission (Aoto et al., 2008). The rate-limiting enzyme for 5-HT synthesis is tryptophan hydroxylase-2 (TPH2) (di Masi et al., 2015d; Yoo and Blackshaw, 2018). Most 5-HT cells are located in the midbrain raphe nuclei (Bang et al., 2012). Extracellular 5-HT level in the brain is tightly controlled by neuronal uptake system at presynaptic nerve endings to maintain a homeostasis.

SERT (serotonin reuptake transporter): a protein encoded by SLC6A4 gene in humans, also known as solute carrier family 6 member 4. SERT is a monoamine transporter protein that transports serotonin from synaptic cleft back into presynaptic neurons via a high affinity Na⁺/Cl⁻ dependent active transport system (Amara and Kuhar, 1993). It terminates effects of serotonin and enables its reuse by presynaptic neurons. SERT is a target of many antidepressant drugs including SSRI and tricyclic antidepressant (TCA) classes.

SSRI (selective serotonin reuptake inhibitor): A class of drugs typically used as antidepressants. Through specifically blocking SERT, SSRI administration selectively enhances 5-HT neurotransmission. Typical SSRI example drugs include fluoxetine and citalopram.

5-HT_{1A} receptor: Long-term antidepressant treatment leads to enhanced serotonergic neurotransmission, likely through action on 5-HT_{1A} receptors (Nemeroff and Owens, 2002). 5-HT_{1A} receptor is the most abundant and widely expressed 5-HT receptor subtype in the brain (Barnes and Sharp, 1999; Beliveau et al., 2017); it both controls 5-HT activity and mediates 5-HT actions (Albert, 2012; Garcia-Garcia et al., 2014).

5-HT_{1A} receptor has dual functions: 1) somatodendritic autoreceptors are located on 5-HT neurons in the raphe nuclei; and 2) postsynaptic heteroreceptors exist on the 5-HT-target projecting non-5-HT neurons (Riad et al., 2001; Vahid-Ansari et al., 2019). Autoreceptors function to negatively regulate 5-HT neuronal firing. 5-HT_{1A} heteroreceptors usually are abundantly expressed in the hippocampus, septum, amygdala and PFC to mediate 5-HT actions on fear, anxiety, stress and cognition (Albert et al., 2014; Garcia-Garcia et al., 2014). Together, 5-HT_{1A} receptors both negatively regulate global 5-HT activity and mediate 5-HT response in target neurons (Vahid-Ansari et al., 2019). Increasing 5-HT_{1A} autoreceptors usually leads to depression-like behavior, whereas knocking-down autoreceptors enhances SSRI responsiveness (Richardson-Jones et al., 2010). Loss of 5-HT_{1A} heteroreceptors, however, usually leads to depression (Samuels et al., 2015).

2. Norepinephrine system:

Norepinephrine (NE) system also plays a pivotal role in the mechanism of antidepressant actions. TCA class of antidepressants and monoamine oxidase inhibitors all elevate synaptic levels of both NE and 5-HT (Laifenfeld et al., 2002). Depressed patients often exhibit lower urinary levels of NE metabolite, the 3-methoxy-4-hydroxy-phenylglycol (MHPG) (Maas et al., 1972).

NE exerts its effects through binding to G-protein coupled α - and β -adrenergic receptors. NE receptors are found on the nerve fibers that originate from locus coeruleus (LC), and project to many parts of forebrain regions including cortex, cerebellum, amygdala, hippocampus and hypothalamus (Maletic et al., 2017). Desensitized α -1ARs are found in the brain of MDD patients, but both affinity and density of inhibitory α 2-ARs are increased in the LC and prefrontal cortex of MDD patients (Garcia-Sevilla et al., 1999; Ordway et al., 2003). Many antidepressant treatments act on overall NE levels (including uptake and MAO inhibitors); or on α -ARs (Montoya et al., 2016). More recent therapies include selective NE reuptake inhibitors such as reboxetine; NE and DA uptake inhibitors such as bupropion; mixed serotonergic and noradrenergic reuptake inhibitors such as venlafaxine and duloxetine (Montoya et al., 2016). The above antidepressants either directly or indirectly modulate NE levels.

NE activity in the LC has been shown to be altered in the brain of MDD patients: with increased levels of tyrosine hydroxylase (TH) and reduced density of NE transporter (NET) in the LC. MHPG concentrations have been shown to be positively correlated with lifetime mood burden, reflecting number, duration and intensity of depressive episodes (Ehnavall et al., 2003).

Long-term SSRI (such as citalopram and escitalopram, paroxetine) administration enhances 5-HT transmission but also exerts inhibitory influence on the NE neurons through enhanced GABA release, resulting in dampened firing activity of NE neurons (Aoto et al., 2008; Dremencov et al., 2007; Szabo et al., 1999). Consequently, lack of therapeutic benefits of SSRI in some depressed patients may result from attenuation of NE transmission even in the presence of 5-HT levels. As a result, attempts have led to more effective augmentation strategies (eg., adding NE reuptake inhibitor in addition to SSRIs) for treating MDD patients not responding to SSRI (Nelson et al., 2004; Seager et al., 2005).

3. Dopamine system:

Dysfunction in the brain dopamine (DA) system has been critically associated with depressive symptoms, such as anhedonia and amotivation (Eshel et al., 2016; Wise, 2004, 2008; Pandit et al., 2016). DA neurons are mainly situated within midbrain, the medial portion of which is in the ventral tegmental area (VTA) (Grace, 2016).

VTA DA neurons project to the reward-related nucleus accumbens (NAc) and ventral striatum (Sesack and Grace, 2010). Animal models of depression like chronic unpredictable mild stress (CUMS) have demonstrated significantly decreased activity in VTA DA neuron populations (Chang and Grace, 2014; Valenti et al., 2012), mainly in medial VTA, which preferentially projects to the reward-related ventromedial accumbens (Ikemoto, 2007; Lammel et al., 2008). Such diminished DA neuronal activity in the medial VTA is likely driven by hyperactivity in the infralimbic prefrontal cortex (ilPFC), which leads to basolateral amygdala (BLA) overdrive and consequently a decrease in the DA neuronal activity via ventral pallidum (VP).

Optogenetically selective inhibition of VTA DA neurons acutely produces depression-related behavior in freely moving mice; whereas phasic activation of VTA DA neurons acutely rescues chronic stress-induced depression phenotype (Chaudhury et al., 2013; Tyte et al., 2013), through altering neural coding of downstream NAc.

A study of learned helplessness rat model of depression has allowed acute induction of anhedonic state and found a rapid reversal by fast-acting antidepressant ketamine (Berman et al., 2000). Half of rats demonstrated “learned” helplessness, who showed a 50 % reduction in the DA neuron population activity and demonstrated a selective attenuation in the excitatory ventral subiculum (vSub)-NAc-VP pathway in control of the amygdala-hippocampal balance. Interestingly, ketamine selectively restored DA neuronal firing activity in those helpless rats, accompanied by normalized vSub-NAc pathway.

The pathophysiology of MDD is also related to disruptions within the DA synthesis system that provides afferent control of DA. Deficits arise within medial frontal cortex and involve amygdala, and also encompass interneuronal dysregulation (Grace, 2016).

Box 2

Open Questions

Can the three brain regions (hippocampus, hypothalamus and orbitofrontal cortex) interact to engage in RA-induced depressive disorder?

This is likely as the hippocampus for instance can exert an inhibitory control over the hypothalamus. Also, the orbitofrontal cortex (OFC) has both input and output connections to the hippocampus. The D2 dopamine receptor in the PFC could be a target for RA (Vincent et al., 1995). The hippocampus could modulate DA function in the mPFC (Peleg-Raibstein et al., 2005), and deficits in the hippocampus can lead to compromised OFC function (Jay et al., 2004; Rocher et al., 2004). Given that altered hippocampal-OFC connectivity plays an important role in the depressive disorder symptoms (Peleg-Raibstein et al., 2005), dysregulation in the hippocampal-OFC circuitry and decreased OFC function could contribute to the RA-associated depressive symptoms (Bremner and McCaffery, 2008). The details regarding to the contribution of OFC dysfunction and interplay of the three brain regions, however, have yet to be explored by animal studies in the future.

Can the three monoaminergic systems (serotonin, dopamine, norepinephrine) interact to mediate the pathophysiology of RA-associated depressive disorder?

Reciprocal interaction exists between the serotonin (5-HT), norepinephrine (NE) and dopamine (DA) system in the brain (De Deurwaerdere and Di Giovanni, 2017; Drago et al., 2011). In vivo studies have confirmed excitatory effect of DA input on the DRN 5-HT neurons, but inhibitory effect of 5-HT input on the VTA DA neurons; as well as reciprocal inhibitory interaction between VTA DA neurons and LC NE neurons (Guiard et al., 2008). In particular, 5-HT receptors may control DA neuronal activity in a phasic, state-dependent and region-dependent manner. Such functional interactions between these three monoamine systems also play an important role in the pathophysiology of depression and in mediating the mechanism of antidepressant actions. However, further studies are required to delineate such mechanisms in detail.

Can hippocampal neurogenesis interact with the monoamine system and play a role in depressive-like behavior?

We believe so. For example, decreased serotonergic signaling could either result in depression-related behavior alone or through affecting adult hippocampal neurogenesis (O'Reilly et al., 2008). The therapeutic effects of many antidepressants acting on the monoamine system often require intact hippocampal neurogenesis (Quesseveur et al., 2013; Santarelli et al., 2003; Yan et al., 2011), further corroborating and emphasizing the importance of interaction of neurogenesis with the monoamine system. Future studies concerning the detailed mechanism will provide with a clearer answer.

Does RA-induced transcription of key molecules play an important role in the pathophysiology of depressive disorder?

We believe so. For example, the transcription factor CREB is shown to be directly and rapidly activated by RA in vitro (Aggarwal et al., 2006; Canon et al., 2004). And the fact that sustained elevation of CREB activity in the nucleus accumbens (NAc) can produce anhedonia-like symptoms (Barrot et al., 2002; Carlezon et al., 1998; Pliakas et al., 2001)) suggests CREB plays a critical role in the regulation of depression (Nestler and Carlezon, 2006).

In addition, long-term targets of antidepressant drugs often include brain-derived neurotrophic factor (BDNF). The important role of BDNF signaling pathway in the VTA-NAc plays in the modulation of depression has also been emphasized (Nestler and Carlezon, 2006). Intra-VTA BDNF exerts a depression-like effect in the NAc, whereas TrkB mutant causes an antidepressant effect (Eisch et al., 2003). RA was found to induce expression of the BDNF receptor TrkB (Kaplan et al., 1993; Kobayashi et al., 1994a). RAR α was able to bind to and trans-activate the BDNF receptor TrkB promoter via a putative RA response element within the TrkB promoter (Qi et al., 2015). Altogether, these above key molecules induced by RA treatment will contribute to RA-associated depressive disorder.

Can we predict a possible antidepressant effect of RAR- α -selective antagonists in clinical use?

Right now, there is no direct clinical evidence that administration of RAR α -selective antagonist could exert therapeutic antidepressant efficacy. However, recent reports have found an antidepressant potential of Ro41-5253 (a selective RAR α antagonist) and demonstrated that Ro41-5253 treatment can ameliorate depressive-like behaviors in the chronic unpredictable mild stress (CUMS) rats (Ke et al., 2019). Future studies will provide a better answer.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2020.02.013>.

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