Review

Defining a vitamin A5/X specific deficiency – vitamin A5/X as a critical dietary factor for mental health

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Abstract: A healthy and balanced diet is an important factor to assure a good functioning of the central and peripheral nervous system. Retinoid X receptor (RXR)-mediated signaling was identified as an important mechanism of transmitting major diet-dependent physiological and nutritional signaling such as the control of myelination and dopamine signalling. Recently, vitamin A5/X, mainly present in vegetables as provitamin A5/X, was identified as a new concept of a vitamin which functions as the nutritional precursor for enabling RXR-mediated signaling. The active form of vitamin A5/X, 9-*cis*-13,14-dehydroretinoic acid (9CDHRA), induces RXR-activation, thereby acting as the central switch for enabling various heterodimer-RXR-signaling cascades involving various partner heterodimers like the fatty acid and eicosanoid receptors/peroxisome proliferator–activated receptors (PPARs), the cholesterol receptors/liver X receptors (LXRs), the vitamin D receptor (VDR), and the vitamin A(1) receptors/retinoic acid receptors (RARs). Thus, nutritional supply of vitamin A5/X might be a general nutritional-dependent switch for enabling this large cascade of hormonal signaling pathways and thus appears important to guarantee an overall organism homeostasis. RXR-mediated signaling was shown to be dependent on vitamin A5/X with direct effects for beneficial physiological and neuro-protective functions mediated systemically or directly in the brain. In summary, through control of dopamine signaling, amyloid β-clearance, neuro-protection and neuro-inflammation, the vitamin A5/X – RXR – RAR – vitamin A(1)-signaling might be "one of" or even "the" critical factor(s) necessary for good mental health, healthy brain aging, as well as for preventing drug addiction and prevention of a large array of nervous system diseases. Likewise, vitamin A5/X – RXR – non-RAR-dependent signaling relevant for myelination/re-myelination and phagocytosis/brain cleanup will contribute to such regulations too. In this review we discuss the basic scientific background, logical connections and nutritional/pharmacological expert recommendations for the nervous system especially considering the ageing brain.

Keywords: vitamin, vitamin A5/X, vitamin D, food, mental health, aging brain

A general introduction of dietary influence on the central and peripheral nervous system functions

A good mental health, a well-functioning central and peripheral nervous system, and the prevention of neurological diseases has been associated with many factors including genetic background ([1] and later summarised with multiple references), individual social background [2], general lifestyle [3, 4] including sufficient physical exercise [5], and sufficient good-quality sleep [6] as well as a stimulating social and family environment [7], in addition to a healthy and balanced diet [8, 9, 10, 11, 12].

It is still not clear what exactly a healthy and balanced diet is and what it does with regard to mental health and a well-functioning brain and for prevention of neurological diseases, especially when considering healthy brain-aging, with relevance for general population convenience and its acceptance in daily life [13]. However, a key factor for a

healthy and balanced diet is the provision of adequate amounts of a variety of foods which will cover the basic requirements for energy, macro-nutrient and micro-nutrient intake in order to sustain the basic metabolic rate, to keep a normal body weight and further additional muscular activities [14]. Malnutrition and over-nutrition leading to substantial body weight loss and obesity, respectively, are not only problematic with regard to the general health of our organism but also for mental health [15, 16].

In addition, a healthy and balanced diet can only be defined as such when being able to maintain (and/or improve) gut-health in terms of guaranteeing adequate bowel movements without gastrointestinal problems and keep the risk low for cancers of the gastrointestinal tract and beyond [17]. However, for people with an unbalanced Western diet – especially with certain gastrointestinal disorders, food allergies, food intolerances or food malabsorption – a composition of healthy and balanced diet may differ from that suitable for healthy individuals and its balancing may require nutritional supplementation. Besides, it is well reported that gastrointestinal disorders are indirectly impacting brain functions and can be associated with mental problems such as anxiety, depression [18] and even eating disorders [19], but also via the microbiota-gut-brain-axis [20].

In this contribution, a comprehensive overview is given on which diets, which specific combination of multicomponent diets, which individual nutrients, which nutrient-deriving ligands or signaling molecules, and which potential signaling pathways may be important for the maintenance of general good mental health, for the general health of the nervous system, for healthy brain aging and the prevention of neurological diseases. In addition, we focus our discussion on the potential health relevance of the newly claimed vitamin, vitamin A5/X. Such health relevance is much based on existing knowledge of functions of retinoid X receptors (RXRs), a documented transcriptional effector of vitamin A5/X-signaling pathways. The emphasis is also placed on the fact that vitamin A5/X is a novel and food dependent pathway with expected high importance for mental health and the prevention of neurological diseases.

Effects of the diet on good mental health and prevention of neurological diseases

In general, a healthy and balanced diet is associated with good health, including good mental health [8, 12]. This notion is strongly supported by scientific data and summarised in expert nutritional recommendations [9, 10] of national and international regulatory bodies, and is generally defined as being rich in fruits and vegetables and low in meat and alcohol. Unfortunately, these recommendations are not widely accepted or applied by a large proportion of the Western society preferring a convenient lifestyle with processed food high in salt, fat and sugar [21, 22, 23]. Even, if a motivated younger and mainly female population in Western society are trying to adapt to general healthy lifestyle recommendations including a healthy diet [24, 25, 26, 27], a much larger percentage of this younger generation as well as the total population, living a westernized lifestyle, still prefers a convenient and unfortunately, not ideally balanced diet [28].

A Mediterranean diet, for example, is a well-accepted diet type by larger groups of societies offering a broad array of valuable nutrients, because of high consumption of fruits and vegetables, olive oil, and marine fish, while a low to moderate consumption of processed food, meat products and alcohol [29]. This Mediterranean diet is an example, as it is more a general life style than a simple food selection, and is also associated with strong social connections and sun exposure, factors which may additionally contribute to such a holistic multicomponent dietary pattern [30] and contribute especially via that social connection also to a healthy food selection instead of a Western single life style associated with a high intake of processed food and alcohol [31].

How such a multicomponent diet transmits its beneficial activity mechanistically, via which food-derived nutrients, via which single or multiple food components and via which pathways is just partially known. Especially when considering a complex combination of these nutrients in the diet which might act via complex interaction pathways in the human organism. Furthermore, many studies just focused on individual single nutrients, how food in general and food enriched with such individual nutrients are interacting within the human organism. These studies were mainly performed in *in vitro* and *in vivo* experimental models to predict how the diet and nutrients transmit potential positive and negative effects within the human organism.

Prebiotics, probiotics and postbiotics acting via the microbiota-gut-brain-axis on mental health and prevention of neurological diseases

Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit to the host [32]. Besides, depending on the mechanism of action, inactivated bacteria or their fractions of probiotics can deliver similar effects, being then defined as paraprobiotics or postbiotics [33, 34]. In contrast, prebiotics are defined as substrates that are selectively utilized by host

microorganisms conferring a health benefit and are characterized by a great variety of substance classes [35]. Historically, probiotics and prebiotics found their application for improving gastrointestinal disorders, delivering mixed results with reasons discussed elsewhere [36, 37, 38]. Therefore, the American Gastrointestinal Association encourages the intake of specific probiotics only for preterm, low birth-weight infants to prevent necrotizing enterocolitis whereas for other gastrointestinal diseases the probiotic intake is either not recommended or conditional (with low quality of evidence) [38].

In short summary, a) as most probiotics are dietary supplements and not drugs, the clinical trials usually do not match the high standards of pharmaceutical trials; b) probiotics differ regarding the number of strains, type of strains and selection method therefore will not have the same efficacy and c) they may not be effective across different patient collectives and patient population subgroups [37]. For prebiotics, the situation becomes even more complex due to the heterogeneity of substance classes (often being fibers) and the variety of exerted effects in the gut [32].

As the gut microbiota also influences the central nervous system via the microbiota-gut-brain axis (reviewed in [20]), therapeutics targeting the gastrointestinal microbiota became of potential interest not only as adjunct treatment of psychiatric and functional central nervous system disorders, but also for modulating mood and stress resilience in health and disease [37, 39]. However, the results on efficacy are very promising in pre-clinical models, the situation in humans is far less clear as recently reviewed [36, 37].

Questionnaire data about the psychological well-being were similar between the probiotic and placebo groups. Only six human studies investigated the impact of probiotics versus placebo using imaging technologies, 5 of them indicated that selected probiotics may alter brain functions in healthy volunteers. However, no conclusions for clinical relevance for patients with respective disorders can be drawn yet [36, 37]. For prebiotics, the current situation is even less clear, due to the lack of imaging studies in humans. Overall, next generation probiotics specifically selected and developed to improve psychiatric condition and potentially other central nervous system functions may be promising [40].

The effect of individual diet-derived nutrients and alternatively consumed substances on mental health

Induction of short- and medium-term effects

Well known compounds used by our society for brain stimulating effects (Figure 1), called nootropics, are accepted consumed compounds present in food such as caffeine and alcohol or are taken up via alternative pathways like **nicotine** [41, 42]. This nicotine uptake originates from smoking tobacco and is applied because of desired stimulating effects on mental status/well-being [43], but its application methods have a strong detrimental health aspect due to oxidative stress [44], deeply ingested radioactivity [45], a large mixture of pro-carcinogenic derivatives [44], and a strong addictive potential towards nicotine [43]. These singular desired and beneficial seen stimulating effects of nicotine result in a quick negative feedback of mental well-being and an addiction towards to get back on "normal" mental well-being with follow up craving for further nicotine stimuli. As a result, this singular positive effect on mental well-being quickly turns into a long term negative mental status followed by an addiction towards smoking as an application method with high toxic burden [44] and an increased risk for neurological diseases [46].

Besides nicotine, **alcohol** is a widely consumed nootropic with a different mechanism of action for inducing positively evaluated effects on mental well-being [47, 48]. In addition, it is an "important" and well accepted part of the daily diet by a large number of humans [27]. The addiction potential and toxicity of alcohol is less severe compared to that of nicotine in tobacco products, although the high number of frequent and heavy drinkers, its relevance in Western society due to the widely used and high consumption of alcohol products is thereby an important public health concern [49].

Caffeine present in coffee, tea, sugary and sweetened soft drinks (like colas) as well as "energy drinks" have also well-known desired positive effects on mental performance [50, 51, 52]. Its addictive and tolerance potential is evaluated as "moderate" in comparison to alcohol, nicotine and other highly active drugs and drug-like substances [50], but its frequent consumption is associated with depression symptoms and anxiety [53]. On the beneficial side, coffee offers a high antioxidant potential [54]. Whether these antioxidant effects may lead to protective functions in the brain is not clear and has not yet been deeply examined in humans as reviewed in [55, 56].

Unfortunately, nicotine, alcohol and caffeine have just short-medium term desired alterating effects on the nervous system, among which are general stimulation and sleep deprivation (caffeine), happiness, decreased anxiety, sociability, impaired cognition-, memory- and sensory-functions, and a generalized depression of the central nervous system (alcohol) and alertness, reduced hunger feeling, reduced anxiety, improved memory and concentration (nicotine).

In addition, there are commonly used, but legally and from society generally non-well accepted non-food substances like **amphetamines** (i.e. 3,4-methylenedioxymethamphetamine (MDMA)/ecstasy (XTC)) [57, 58],

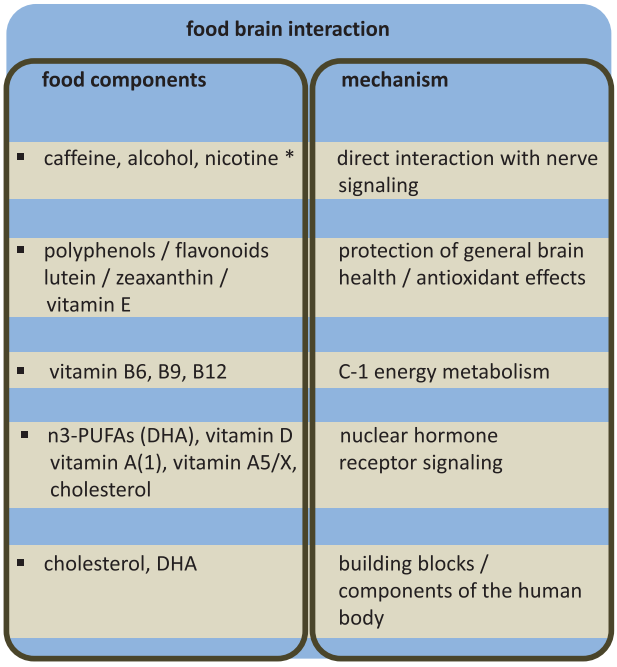

Figure 1. General mechanisms of how food interacts with brain health. *Representing a non food, but alternatively consumed substance.

cocaine [59] **and cannabinoids** [60, 61] which have short time "desired" effects of enhancing nervous system functions which are associated with unwanted strong addictive potential and negative side effects. These short term "desired" effects on brain functions further induce non-desired feedback mechanisms in the neuro-physiological pathways especially in the vitamin A5/X – RXR-mediated signaling pathways [62, 63].

In this context, RXR-signaling, induced also by vitamin A5/X, may have a beneficial effect in fighting addiction to these substances like recently suggested by Godino et al. 2023 [62, 63]. In addition, the craving to other substances with addiction potential like the previously mentioned substances as well as general nutrients like **fat** and **sugar** with food intake dopamine-motivation feedback [64, 65, 66] is directly or indirectly controlled by RXR-mediated signaling due to transcriptional control of dopamine receptor's expression [67].

Induction of latent and/or long-lasting effects

In contrast, there are nutrients with long term general beneficial health effects on the central and peripheral nervous system [10, 12, 13, 68]. These are derivatives which do not functionally interact with the nervous system-signaling with immediate and quickly observable effects on the central nervous system. These nutrients mainly influence brain development, general maintenance of nervous system- signaling, neuronal regeneration, a general well-functioning nervous system, inflammatory processes systemically or directly within the brain, proteostasis, and the maintenance of brain performance such as cognition/memory but with no observable tolerogenic and addictive potential. Thereby, their potential for improving the general mental well-being seems to be mainly based on a general maintenance or protection of a healthy maintenance of the nervous system via enabling an organised homeostatic general macronutrient supply. They additionally function itself as macronutrients or precursors being itself building blocks/components of the nervous systems [69], or being required for physiological-balanced regulation pathways of nervous signaling and a balanced local nervous system-based inflammatory process.

The mechanisms of such pleiotropic activities of nutrients are diverse. An antioxidant response is part of this protection for a healthy maintenance of nervous system functions [10]. Here the classical antioxidants are acting mainly systemically like **vitamin C** [70], **vitamin E** [71, 72], **polyphenols** [73, 74] and **flavonoids** [75, 76] as well as local acting antioxidants within specific brain areas like the **non-provitamin A carotenoids lutein/zeaxanthin** [77, 78] are involved in such general antioxidant protection. Furthermore, **cholesterol** [79] and the **n3-fatty acid docosahexaenoic acid (DHA)** [80, 81] are building blocks/components of cellular membranes [69], but also studied as direct physiological activators or precursors of bioactive molecules enabling optimal nervous system signaling in the central and peripheral nervous system [82, 83, 84]. Further derivatives like **vitamin B12, B6, and folate (vitamin B9)** are involved in C1-body physiology, which is of importance for a general energy homeostasis in the peripheral nervous system and brain [85, 86]. These listed compounds are involved in neural functions and thereby their deficiency is associated with dysfunctions of the central and peripheral nervous system [87]. These compounds are required in sufficient amounts in the daily diet [88].

A number of micronutrients act also as ligands for nuclear hormone receptor (NHR) mediated-signaling to control transcriptional regulation of basic homeostasis of the human organism, but also adaptive responses. Thus nervous system homeostasis and its optimal performance requires balanced signaling via the peroxisome proliferator-activated receptors (PPARs) with fatty acid-metabolites or fatty acids like the **n3-fatty acid/DHA** as ligands [84], the liver X receptors (LXRs) with **cholesterol derivatives** as ligands [89], the vitamin D receptor (VDR) with **vitamin D derivatives** as ligands [89] and the retinoic acid receptors (RARs) with **vitamin A(1)/pro-vitamin A(1) carotenoids** as precursors for all-*trans* retinoic acid as the ligand, for which a physiological homeostatic regulation is of physiological and homeostatic importance [90, 91, 92,

93]. Even additive or "boosting" effects of supplementations with selected nutrients like DHA can be observed when applied beyond recommended daily intake amounts for better nervous system functions [80, 94, 95, 96, 97]. Crucial partners for such nuclear hormone receptor mediated signaling are the retinoid X receptors (RXRs), as they act as obligatory heterodimerisation partners for several alternative nuclear hormone receptors to enable their binding to DNA and further individual transcriptional activities. In this review we will focus on these RXR-dependent pathways involving the newly found endogenous RXR ligand and its recently identified nutritional precursors [98, 99]. These compounds represent novel physiologically important factors for the central and peripheral nervous system, requiring an optimal diet for maintenance but also offering possibilities for boosting beneficial effects following additive supplementations beyond the advised recommended amounts [99, 100, 101, 102, 103, 104].

Effects of provitamin A(1) and vitamin A(1) on mental health and prevention of neurological disorders

Provitamin A(1), such as β-carotene and alternative provitamin A(1) carotenoids, in addition to vitamin A(1) alcohol, such as all-*trans*-retinol (ATROL), and its esters are the major relevant food derived precursors of all-*trans*-retinoic acid (ATRA)/vitamin A(1)-acid as the endogenous ligand of the RARs (Figure 2, [102]). RARs act as transcription factors controlling a wide range of RAR-response pathways [102, 103]. Relevant RAR-response proteins are involved in an array of crucial physiological processes like differentiation, proliferation, apoptosis, metabolism, inflammation and an overall macro- and micro-nutrient homeostasis [102, 105]. Various proteins are thereby directly involved in a general homeostasis of macro- and micro-nutrient nutrikinetics systemically, but also within the nervous systems [90, 106, 107], like for structural proteins [108, 109, 110], proteostasis with relevance for amyloid aggregates [111, 112, 113], developmental processes and neurogenesis within the brain. These proteins have important functions with respect to growth and plasticity of various cells types within the brain, including neurons [114, 115, 116], astrocytes [117, 118], oligodendrocytes [119, 120, 121], and microglia [122, 123, 124] as well as being enzymes and receptors enabling homeostatic synaptic plasticity [125, 126].

In general, a **primary vitamin A(1) deficiency** [127, 128] refers to insufficient nutritional vitamin A(1) intake and in real life is mostly associated with low intake of vitamin A(1)/provitamin A(1), while a **secondary vitamin A(1) deficiency** is the notion which refers to decreased activity of vitamin A(1)-mediated signalling in the organism which is a result from dysfunctional or compromised vitamin A(1)-uptake, bioactivation/metabolism as well as vitamin A(1)-RAR-mediated signaling through its receptors and associated factors.

In such a primary vitamin A(1)-deficiency often, an insufficient intake of additional macro- and micro-nutrients co-occurs. This condition is encountered mostly in developing countries of Africa and South-East Asia. The World Health Organization (WHO) reports that in these regions 250 million preschool children suffer from insufficient vitamin A(1) intake and 500,000 of these children become blind. Vitamin A(1) deficiency, resulting from selective insufficient vitamin A(1) intake or general insufficient micro- and macro-nutrient intake [129], is life-threatening and causes death of about 250,000 children, mainly because of immune deficits. Despite these facts there are no dedicated studies on neurological effects of vitamin A deficiency in these populations.

In the Western society reduced blood levels of vitamin A(1) are associated with biological aging [130, 131], although some studies did not detect any significant changes [132, 133]. Such discrepancy may reflect – at least partially – heterogeneity of data resulting from differences in inclusion criteria of these studies. For example, analyses of an aged population assessing their cognitive performance revealed that individuals with compromised learning and memory capacity displayed lower levels of ATROL/vitamin A(1)-alcohol [134, 135]. Such data suggest that low vitamin A(1) levels may be causally associated with cognitive deficits [136], which is further supported by rare clinical trials and animal studies. Accordingly, aged rats displayed decreased levels of ATROL and ATRA, which were correlated with compromised learning and memory [137, 138]. Such deficits were observed in the hippocampus, the structure directly involved in learning and memory. Importantly, aged rats or mice displayed also reduced expression of several retinoid receptors in the same brain region, which could further contribute to deficits in vitamin A(1)-signaling and underlie thereby learning and memory deficits associated with aging [132, 139, 140, 141]. Such dysfunctional or compromised vitamin A(1)-signaling can be defined as a **secondary vitamin A(1) deficiency** [128]. In support of this hypothesis, both, the selected aging related molecular changes and the memory deficits could be prevented or normalized by chronic or acute treatments with vitamin A(1) or selected retinoids [137, 138, 142].

In addition to aging-related cognitive deficits, compromised vitamin A(1) signaling was also observed in several neurological conditions. In the case of Alzheimer's disease (AD), a reduced retinaldehyde-dehydrogenase 2 (Raldh2/ALDH1A2, a key enzyme synthesizing ATRA) expression and lower ATRA production was observed within specific brain regions [143, 144]. Amyloid beta (Aβ) was shown to

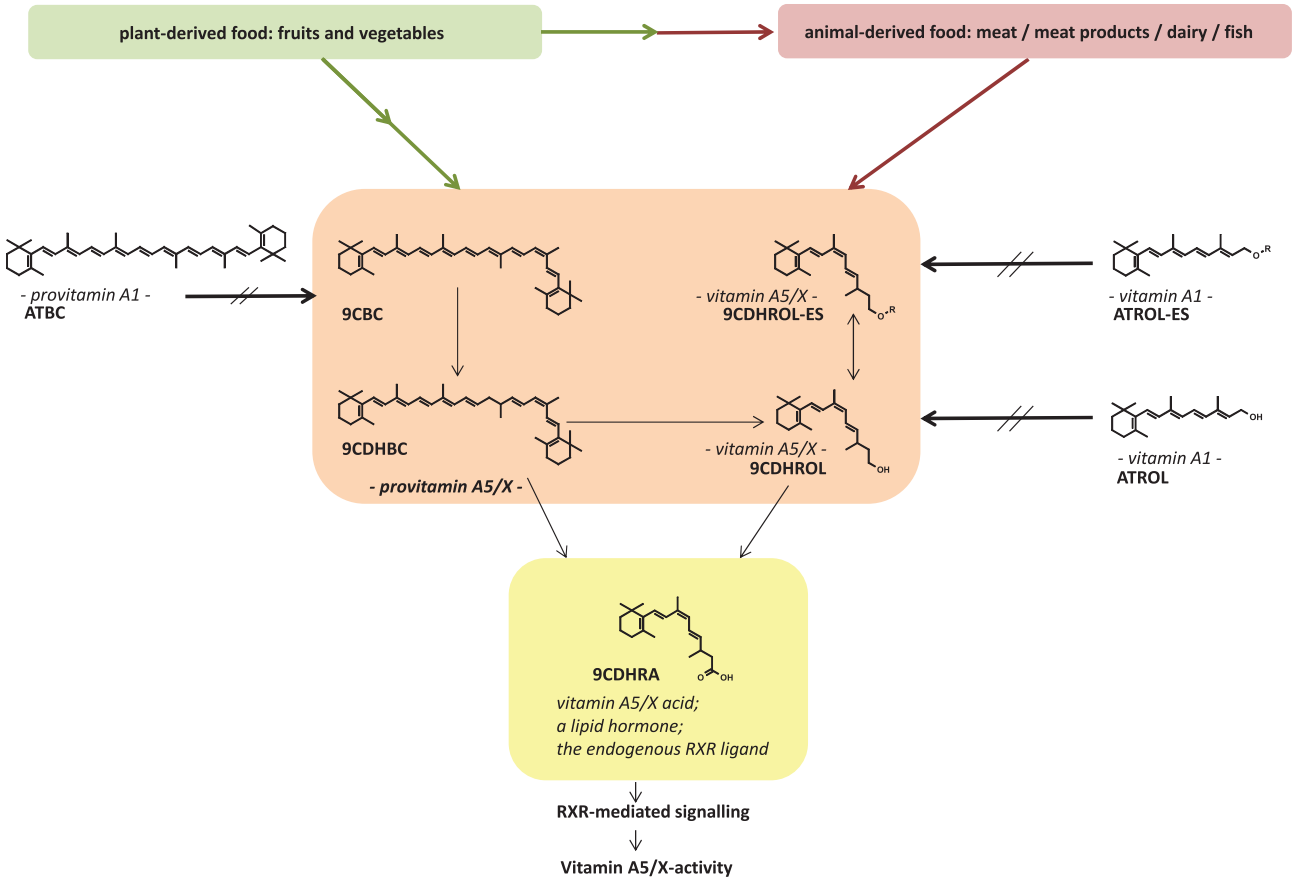

Figure 2. The vitamin A5/X concept: Summarized are the metabolic pathways of vitamin A5/X / provitamin A5/X starting from nutritionally-derived retinoids and carotenoids towards RXR-mediated signaling. *Abbreviations:* ATROL-ES: all-*trans*-retinyl esters; ATROL: all-trans-retinol; ATBC: all-*trans*-β,β-carotene; 9CDHROL-ES: 9-*cis*-13,14-dihydroretinyl esters; 9CDHROL: 9-*cis*-13,14-dihydroretinol; 9CDHBC: 9-*cis*-13,14-dihydro-β,β-carotene; 9CBC: 9-*cis*-β,β-carotene; 9CDHRA: 9-*cis*-13,14-dihydroretinoic acid.

further compromise vitamin A(1)-signaling by downregulation of retinoic acid receptor α (RARα) expression, synergizing thereby with lower (blood) ATRA levels in inducing memory deficits. Reduced levels of vitamin A(1) in form of ATROL in blood were also reported in plasma of AD-patients [145, 146]. A significant involvement of compromised ATRA signaling in AD is supported by deposition of Aβ aggregates in vitamin A(1)-deficient rats [143] and beneficial effects of ATRA treatment including anti-inflammatory and neuro-protective effects as well as inhibition of Aβ aggregates deposition [107, 141].

Compromised synthesis of ATRA was also suggested to be associated with Parkinson's disease (PD). Indeed, several reports described reduced expression of retinaldehyde-dehydrogenase 1 (Raldh1/ALDH1A1, an alternative enzyme synthesizing ATRA), by midbrain dopaminergic neurons in PD patients [147, 148, 149]. In fact, Raldh1 is one of the specific markers of a subpopulation of those neurons [150] and its reduction in PD was associated not only with loss of these neurons, but also to be reduced in remaining dopaminergic neurons [147, 148]. Similarly, a combined genetic ablation of murine Raldh1 and retinol-dehydrogenase 5 (Adh5), a further rate-limiting enzyme to synthesize retinaldehyde from vitamin A(1)/ATROL, leads to progressive motor deficits and loss of dopaminergic neurons [151]. In this context, several controlled or prospective studies explored the possibility, that reduced intake of vitamin A(1) or provitamin A(1) may act as sensitivity factor to develop PD. Whereas most of these studies did not provide any clear correlation [152, 153, 154, 155]. Furthermore, Yang et al. 2017 [156] reported that increased consumption of β-carotene/provitamin A(1) from a natural diet is associated with a reduced rate of PD prevalence.

Locomotor deficits and reduced signaling of dopaminergic receptors in the striatum, was reported in RARβ-/- null mutant mice and in compound RARβ-/-; RXRγ-/- null mutant mice [101, 157]. A recent transcriptome analysis of the striatum of RARβ-/- mice, and combined with genome-wide identification of RARβ-binding sites using high-throughput chromatin immunoprecipitation (ChIPseq) [158], pointed to several mechanistic hypotheses for neuroprotective activities of RARβ. Collectively, these data

suggest a strong contribution of RARβ in controlling neurotransmission, energy metabolism (with a particular involvement of G-proteins), cAMP and calcium signaling. Striatum related activities of RARβ might be of special importance for understanding the pathogenesis of Huntington disease, a rare disease in which RARβ expression was found reduced ([158, 159] and references therein).

Effects of the sunshine vitamin, vitamin D, on mental health and prevention of neurological diseases

In the last years, there is an increasing attention towards vitamin D for mechanisms of action involved in immune response, cardio-vascular functions as well as an active involvement in the nervous system [160, 161]. In general, vitamin D in the form of vitamin D_2 and mainly as D_3 (ergocalciferol or cholecalciferol) can be taken up by the diet or synthesized by UV-irradiation from 7-dehydrocholesterol (provitamin D_3). This vitamin D, especially vitamin D_3, is further metabolized to 25-hydroxy-vitamin D_3, which is homeostatically regulated and transported in the blood, while the further active vitamin D derivative is 1,25-dihydroxy-vitamin D_3/1,25$(OH)_2VD_3$ [162]. This active vitamin D_3 derivatives binds, similarly to the active vitamin A(1) and vitamin A5 derivatives, to specific nuclear hormone receptors which control transcriptional regulation via DNA binding [89, 163]. For this vitamin D-mediated regulation the nuclear hormone receptor, the vitamin D receptor (VDR), must be ligand activated by the active vitamin D derivative 1,25$(OH)_2VD_3$ [162]. This liganded and thereby activated VDR needs further the retinoid X receptor (RXR) as a dimerization partner for DNA-binding and for regulation of vitamin D-mediated transcriptional regulation [163, 164]. Many studies favor the fact, that this VDR-RXR complex can exclusively be activated by the VDR-ligand [89, 163, 165], although alternative studies confirm activation via the RXR partner additionally [166]. Recent data describe a correlation of the active VDR-ligand as well as the active RXR-ligand present in human serum with a vitamin D-regulated immune target also present in human serum samples [167].

Vitamin D-mediated signaling occurs in various organs of the mammalian organism and regulates a large array of physiological mechanisms [168]. Here also many pathways involving the VDR in the general maintenance of the nervous systems are of high importance, especially during development of the nervous system [161, 169, 170], highlighting a sufficient nutritional intake of this vitamin being important for good mental health and the prevention from a large array of neurological disorders like psychiatric/psychotic, neurodegenerative and demyelinating diseases [171, 172, 173, 174].

Nutritional supplementation with vitamin D seems to be of high importance as vitamin D intake appears to be below the suggested dietary recommendations in Western society [27]. Many supplementation studies with sufficient vitamin D amounts [172, 175] or with vitamin D amounts beyond the recommended daily dietary levels were shown to be beneficial taken either alone or in combination with additional nutrients, like the previously discussed B-vitamins and n3-PUFAs [176, 177]. Unfortunately, many supplementation studies showed no improvement on mental health, reviewed in [178].

In summary, sufficient vitamin D intake seems to be related to good mental health and the prevention of neurological diseases mainly mediated via RXR – VDR-mediated signaling pathways. A dietary supplementation, food fortification and at its best a healthy balanced diet seems to be beneficial for human health considering the risk of a low basic vitamin D intake and low sun exposure. If at conditions with optimal sufficient vitamin D intake and status, an additional vitamin D supplementation is needed and beneficial on the long term, seems to be questionable.

Macronutrients and mental health

Macronutrients like fat and carbohydrates are a broad group of compounds in the human diet mainly functioning as construction material for the human organism with focus here on brain/nerves, as energy providing precursors as well as important precursors for hormone regulatory pathways in our human organism. These functional derivatives are further involved in the control of various pathways for communication between the human organism and the nervous system especially to control energy homeostasis via a hunger/satiety regulation mainly via interaction within the human brain [179, 180].

The main food-derived macronutrients are of complex macromolecular structures like polysaccharides and complex lipid structures. These compounds are metabolized in the human organism to smaller units such as simple sugars/monosaccharides and non-esterified free unbranched fatty acids, which are also directly ingested with the diet but in much smaller quantity. However, smaller molecules can be used to build up larger macromolecules, which are needed in our organism as crucial construction materials, while, more interestingly, in the present case as bioactive molecules like various hydroxyl-metabolites of DHA [181, 182].

Monosaccharides are key substances for energy metabolism and seem also to be recognized by specific areas within the human brain [183]. This brain-nutrient interaction is an important regulator of selective food intake and homeostatic regulation, while also dopamine feedback cascades are involved [184]. At this level monosaccharide levels

and its feedback regulation on selective craving/hunger/satiety is among others also controlled via vitamin A5 – RXR-mediated signalling [67]. Thereby, these macronutrients like fat and sugar have also an addiction potential, as dopamine-motivation feedback is triggered [64, 65, 66]. This feedback regulation is highly depending on the individual ingestion of a food with parameters such as food quantity, diet composition, and individual dietary requirements [185]. In several studies it was shown that added carbohydrates in the human diet are negatively associated with individual mental health [185]. Especially food rich in monosaccharides like fructose and glucose seems to be here of relevance [186]. Fructose ingestion is directly interacting with the brain in further hormonal regulation [187] and further modification of incidence of depression [188] or depressive-like behavior [189]. This involves the dopamine-mediated reward signaling and the inhibition of the neurotransmission controlled by γ-aminobutyric acid (GABA) [64].

Sugar-sweetened beverages and "fast food" consumption high in carbohydrates and fat are often part of clustered food patterns, thus, more negative synergistic effects on the whole human organism and especially our mental health can be expected [190]. Besides these direct effects on mental health a continuous excess of sugar and fat in our diet impairs glucose and lipid metabolism and promotes general and local inflammatory processes [191] with an indirect negative impact on mental health.

An additional pathway involved is the feedback regulation of insulin secretion being also regulated by vitamin A5 – RXR-mediated signalling pathways [192, 193]. Insulin directly interacts within specific brain areas and is thereby responsible for controlling food intake and regulating cognitive functions, particularly memory [194]. An excess of free saturated fatty acids leads to a dysregulation of glucose homeostasis and insulin resistance with its consequence described above [195]. Moreover, the free saturated fatty acids affect cognitive function with ending in diseases such as dementia, including Alzheimer's disease [196].

In summary, macronutrients especially carbohydrates/sugars as well as fats/fatty acids are also directly involved in mental well-being with positive and negative effects depending on the individual dietary intake via control of insulin-secretion and dopamine-signalling regulation of these direct and indirect macronutrient-induced pathways which are also co-regulated by vitamin A5 – RXR-mediated signalling.

A general summary of food for brain health

In summary, based on various studies and summarizing review articles we can conclude that these various dietary factors individually or as composites of a general holistic approach with a healthy and balanced diet are of importance for a good functioning of the central and peripheral nervous system, although in many cases the mechanisms of action are not clearly identified. A general relevance of specific micro- and macro-nutrient deficiencies in developing/low-income countries and societies within the Western society with general food shortage are well documented [197]. For a large array of these nutrients a dietary deficiency must be compensated by an adequate diet or by fortification of a Westernised diet low in these nutrients to recover from a deficiency syndrome likely relevant for B-vitamins, D-vitamins and antioxidants. Other nutrients can ameliorate a specific deficiency but also partly induce desired boosting/"plus"-activities on brain performance and general functions of the central and peripheral nervous system like observed for n3-fatty acids and vitamin D [80, 94, 95, 96, 97] and also predicted for vitamin A5/X derivatives [99, 101].

Specifically, a primary and secondary vitamin A(1) deficiency is associated with dysfunctional or compromised functions of the central and peripheral nervous system resulting in various indicators of non-optimal mental health like mental stress, anxiety, depression, cognitive decline, nervousness, as well as in consequence, due to the involved signaling pathways, a general loss of enjoyment of life, irritability, insecurity, dissatisfaction, listlessness in addition to a higher prevalence of drug addiction and an increased incidence of neurological diseases [106, 107].

Vitamin A5/X in nutrition and mental health

The general vitamin A5/X concept

In 2015, 9-*cis*-13,14-dihydro-retinoic acid (9CDHRA) was identified as the endogenous ligand for the retinoid X receptors (RXRs) with an overlapping endogenous/nutritional-relevant concentration range sufficient to switch "on – off" RXR-mediated signaling (Figure 2, [102]). Due to its similar structure to vitamin A(1) it was suggested to be sub-ordinated to vitamin A as vitamin A5 [198]. Alternatively due to its distinct mechanisms of action it may be described as an individual new group of vitamin, named vitamin X [98, 99, 198]. Various other endogenous RXR-ligands were already identified with questionable physiological/nutritional relevance profile [84, 199] indicating, that 9CDHRA is the most likely relevant physiological/nutritional RXR ligand [102].

The biological occurrence of 9CDHRA was later found to be independent of vitamin A(1) nutritional precursors like retinol/retinyl esters and provitamin A(1) carotenoids [99]. The endogenous occurring and nutritional-relevant

direct precursor 9-*cis*-13,14-dihydroretinol (9CDHROL) was identified and associated as vitamin A5/X, a vitamin A(1) independent source for 9CDHRA and enabling vitamin A5/X-receptor (RXR)-mediated signaling [99]. In parallel, to 9CDHROL, as vitamin A5/X-alcohol, present in animal derived food sources [99] we also identified 9-*cis*-13,14-dihydro-β,β-carotene (9CDHBC) and its nutritional precursor 9-*cis*-β,β-carotene (9CBC) as plant derived precursors [99] (Figure 2). Unfortunately, the involved binding proteins and enzymes in the metabolic pathways have not been identified until now in detail. We assume a high overlap with binding proteins/enzymes of the vitamin A(1) metabolic pathway due to a high similarity of vitamin A5/X derivatives especially considering 9-*cis*-retinoids [102]. Due to the similarity in vitamin A(1) and vitamin A5/X physicochemical features and possibly metabolic pathways designing nutritional models specific to vitamin A5/X pathway for detailed analysis of metabolic, physiological and nutritional functions might be impossible to distinguish. Although genetic manipulations like ablation of retinol binding protein 1 (Rbp1) is a more plausible approach, it will require identification of other molecular actors of vitamin A5/X metabolic pathway.

Functional relevance of enabling vitamin A5/X – RXR-mediated signaling was demonstrated by enhancement of cognitive functions [99], as well as, prevention of depressive-like behaviours in response to chronic stress [101] in an RXR-dependent manner. In consequence a new food derivative to specific food component associated function was identified, proven, patented and published [198] for further valorisation in food- and pharma-applications.

In summary, the nutritionally-relevant vitamin A5/X derivatives like 9CDHROL and 9CDHROL-esters as well as provitamin A5/X, 9CBC via 9CDHBC, act as direct precursors of the active vitamin A5/X-ligand 9CDHRA. This 9CDHRA can directly modify RXR-mediated signaling via interaction with optional nuclear hormone receptor as partner of different heterodimers and thereby further induce transcriptional alteration of targeted gene regulation. In consequence, the term vitamin A5/X indicates all food derived substances, which are proximate precursors of 9CDHRA and are thereby modifying proximately RXR-mediated signaling.

Relevance and function of vitamin A5/X – RXR-mediated signaling

RXRs are crucial binding partner for other heterodimer-partners of nuclear hormone receptor (NHR) group [98, 163, 200, 201, 202] and functions as the vitamin A5/X receptor. Among these NHRs, here we mainly focus on the most relevant ones with a "health"- and "food"-application potential like the RARs, PPARs, LXRs, VDR and the NR4A2 (Figure 3), all known to be involved in NHR-signaling pathways with relevance for the human health.

This RXR-mediated signaling is of importance for various general physiological pathways like cell differentiation, general development, embryogenesis, cell cycle regulation, apoptosis, and systemically specific pathways like general inflammation/immune response, micro-circulation/enabling sufficient blood flow, the general lipid and glucose metabolism [200, 202] as well as brain-specific pathways like control of dopamine signaling [203], neuro-protection [204], control of local inflammation [205, 206], and Aβ-clearance [207]. These general and brain-specific physiological pathways are not singularly regulated by one specific RXR heterodimer, but most probably in a complementary manner by different RXR heterodimers including in particular RAR-RXR heterodimers and are thereby likely dependent on sufficient nutritional vitamin A(1) and vitamin A5/X supply, as outlined in Figure 3.

Recently these dietary intake suggestions for vitamin A5/X were calculated to be in the range of 0,5–1,8 mg provitamin A5/X per/day for healthy adults [198], which corresponds to ∼1 mg provitamin A5/X / 400 g of general mixed vegetables. This is exactly in the range of the suggested "5 A Day" recommendations by the World Health Organization (WHO) [208], the UK National Health Service (NHS) [209] and the German Nutrition Society (Deutsche Gesellschaft für Ernährung, DGE) [210], when "one hand full of fruits and vegetables" weights ∼80 g of these food components [208], resulting in the five suggested handful portions calculated by this simplified approach.

Other functions are independent of RAR–RXR-signaling and thus exclusively regulated by vitamin A5/X-dependent RXR – "plus other NHR"-pathways. Examples are hair development, mainly regulated via RXR – VDR pathways [211], while cholesterol efflux [212], local brain phagocytosis/brain cleanup [205, 213] and myelination/re-myelination [120] are LXR – and PPAR – RXR co-mediated pathways [213, 214, 215] (Figure 4).

This puts vitamin A5/X and the RXRs, as the vitamin A5/X-receptors, in the center and as the major switch enabling nuclear hormone receptor mediated signaling via activation of RXR as part of NHR-heterodimers, thereby, enabling a larger array of NHR-mediated signaling pathways ranging from RAR-, PPAR-, LXR-, VDR- and NR4A-mediated signaling pathways [89, 163]. The RXR-mediated pathways were reviewed recently by Evans and Mangelsdorf [202], who actually pointed out ligand-dependent control of RXRs as a "Big Bang" of molecular endocrinology. However, as summarized in various review articles [84, 99, 102, 198] and based on analytical data [98], 9CRA initially put forward as "the" physiological RXR ligand in the mammalian organism is highly questionable. Therefore, the vitamin A5/X-acid, 9CDHRA, appears as

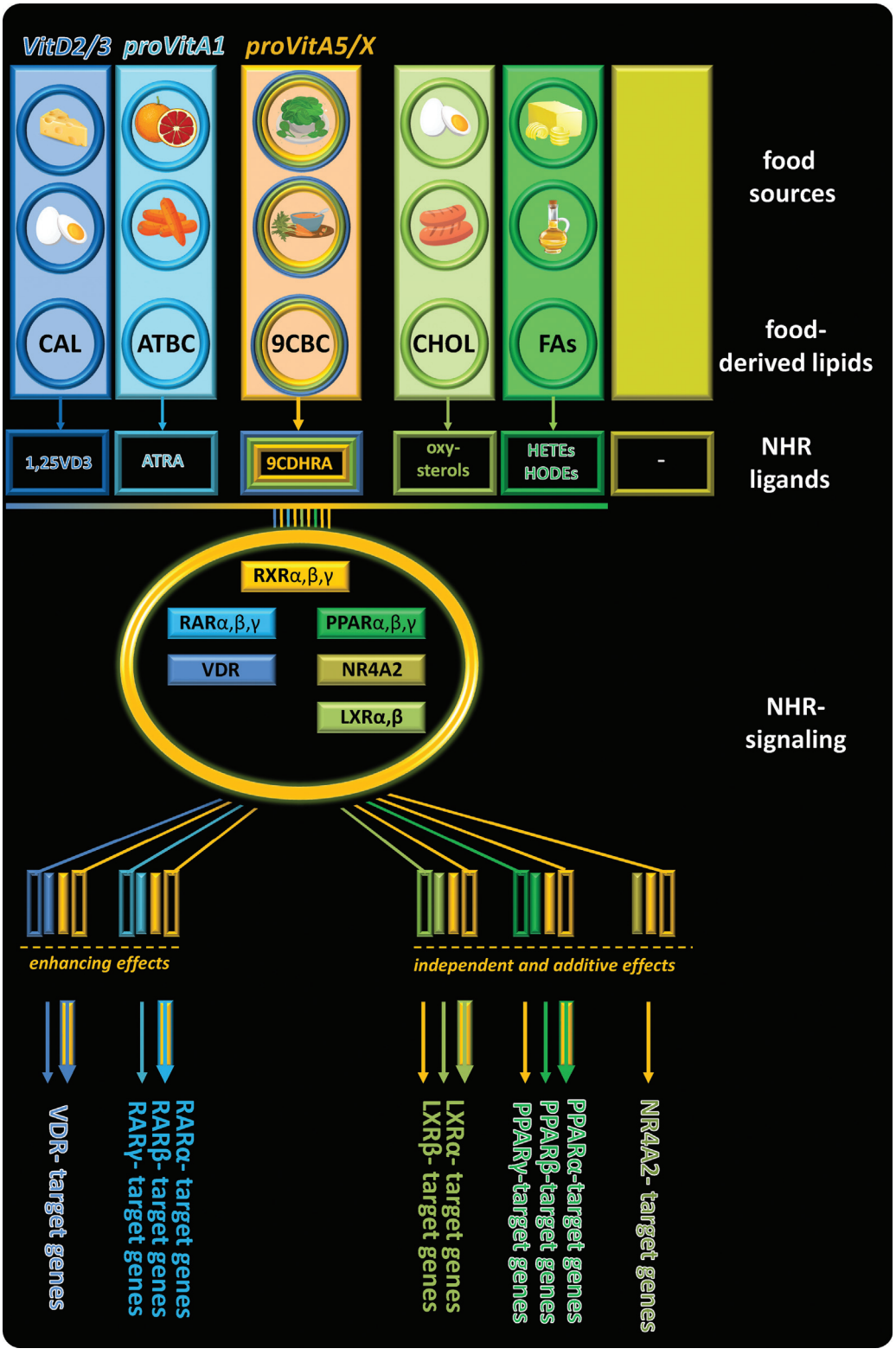

Figure 3. Nuclear hormone receptor (NHR) signaling pathways involving retinoid X receptors (RXR)-mediated signaling and are initiated by the endogenous RXR-ligand, 9-*cis*-13,14-dihydroretinoic acid (9CDHRA). *Abbreviations:* VitD2/3: Vitamin D2/3; proVitA1: provitamin A1; proVitA5/X: provitamin A5/X; CAL: calcitriols; ATBC: all-*trans*-β,β-carotene; 9CBC: 9-*cis*-β,β-carotene; CHOL: cholesterol; FAs: fatty acids; 1,25VD3: 1,25-dihydroxy-vitamin D3; ATRA: all-*trans*-retinoic acid; HETEs: hydroxy-eicosatetraenoic acids; HODEs: hydroxy-docosahexaenoic acids; PGs: prostaglandins; VDR: vitamin D receptor; RARs: retinoic acid receptors; LXRs: liver X receptors; PPARs: peroxisome proliferator-activated receptors; NR4A2: nuclear receptor subfamily 4 group A member 2.

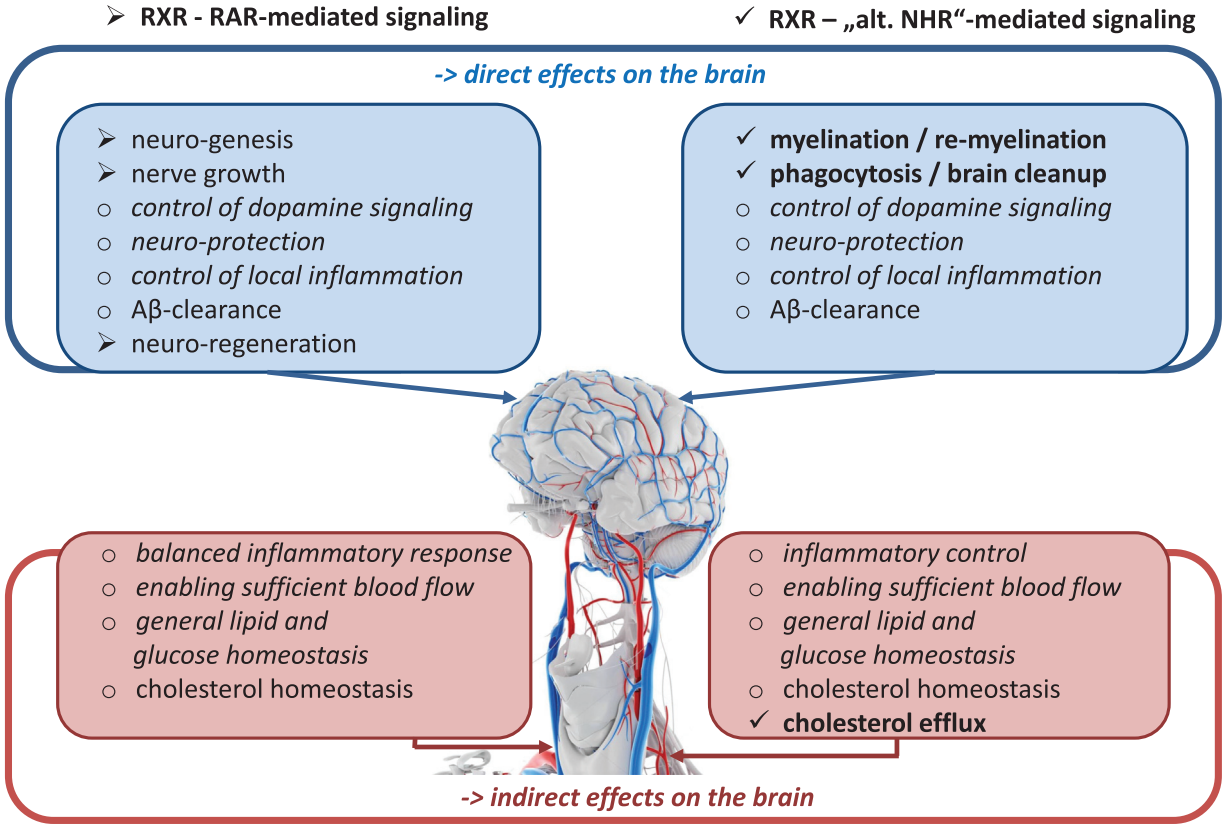

Figure 4. Direct and indirect effects of RXR-mediated signaling on brain and nervous systems functions. *Abbreviations:* RAR: retinoic acid receptor; NHR: nuclear hormone receptor; Aβ: amyloid β; alt: alternative.

the most likely physiological ligand of RXRs, as the vitamin A5/X receptors, placing vitamin A5/X as the nutrition-dependent spark, including further vitamin A5/X – RXR-mediated signaling, for the real "Big Bang" in human life [102, 198].

A large array of physiological processes is thereby enabled by vitamin A5/X summarized in an evolved figure 4 shown in our previous article [198]. Physiological processes like cholesterol homeostasis, bile acid homeostasis, fatty acid homeostasis, xenoprotection, basal metabolic rate, calcium- and phosphate-homeostasis, and development are vitamin A5/X – RXR-co-regulated physiological pathways important for a large array of important life remaining functions within a mammalian organism.

Physiological- and nutritional-relevance of RXR-mediated signalling in the brain

Retinoid signaling, particularly RXR-mediated pathways, play a crucial role not only during development of the central and peripheral nervous system, but are also involved in various maintenance functions of the adult central nervous system. Besides the pivotal involvement of RXR-mediated signaling in the modulation of immune-mediated processes [201, 216, 217, 218], these RXR-dependent pathways have been found to be involved in neuronal homeostasis at various levels. These various physiological events in the central and peripheral nervous system, that depend on RXR-mediated signaling are thus likely dependent in consequence on a nutritional supply of vitamin A5/X compounds [99].

A large array of physiological events directly and indirectly relevant for the central and peripheral nervous system are mediated by RXR-mediated signaling (Figure 4). Further, we evaluated and focussed on physiological events, which are non-RXR – RAR-mediated. At the first step, in summary, we started evaluating the large number of physiological events which are multifactorial and rely on RXR – RAR-mediated signaling as summarised in Figure 4, while specific events like myelination/re-myelination and local phagocytosis/pathogen clearance as brain cleanup are exclusively non-RXR – RAR-dependent involving alternative NHR heterodimers.

Examples of such RXR-dependent activities is neuro-protection of dopaminergic neurons, through activation of RXR – NR4A2 heterodimers [219, 220], or neuro-protection of retinal ganglion cells by RXR heterodimers with a yet unknown partner [221]. Ligand-induced activation of

RXRs was also demonstrated for enhanced macrophage/microglia-mediated clearance via phagocytosis as brain cleanup of myelin debris [222] or clearance of neuronal debris following stroke [205]. Finally, macrophage or microglia RXR-activation was also demonstrated to minimize inflammatory signaling which is detrimental in a number of neurologic conditions [223, 224].

In summary, these mechanisms are exclusively focusing on the peripheral and central nervous system are a) myelination/re-myelination, b) dopamine receptor 2 (D2DR) expression control and thereby a general regulation of dopamine signaling, c) brain specific phagocytosis with general relevance for brain cleanup, d) neuro-inflammation, e) general neuro-protection and f) Aβ-clearance, as summarised in Figure 4 and as further discussed.

While RXR-signaling will here regulate direct targets in the brain, indirect pathways are also of relevant with an impact on the brain, although mediated on a systemic basis. These are: a) general nervous tissue-located glucose and lipid homeostasis, b) enabling sufficient blood circulation in the microvascular system of the brain, c) systemic lipid and glucose homeostatic control and d) a local and systemic regulation of the inflammatory response with a large focus on Th1-Th2-regulation [225, 226, 227].

In summary, directly brain-mediated as well as general systemically-regulated mechanisms dependent on vitamin A5/X – RXR-mediated signaling are important for a healthy maintenance of crucial functions of the central and peripheral nervous system with relevance for mental health, healthy brain aging as well as protection from drug addiction and from various neurological disorders.

Pathology of dysfunctional vitamin A5/X – RXR-mediated signaling in the nervous system with relevance for neurological disorders

As described earlier, various pathways involving RXR-mediated signaling are directly and indirectly relevant for the central and peripheral nervous system. Furthermore, we focus on the mechanisms involved in neurological diseases, which are probably caused not just by one single dysfunctional mechanism but by a broader array of multiple underlying mechanisms. However, neurological diseases like a) mental/psychotic diseases, b) neurodevelopmental diseases, c) neurodegenerative diseases, d) demyelinating diseases and e) neuro-inflammatory diseases have been associated with dysregulation of vitamin A5/X – RXR-mediated signaling (Figure 4).

RXR-mediated signaling has been linked at multiple levels to neurodegenerative diseases, such as Alzheimer's and Parkinson's disease [228, 229, 230], inflammation- and demyelination-associated disorders such as the various forms of multiple sclerosis and neurological disorders with a pathophysiological basis in atherosclerosis, including stroke and vascular dementia, reviewed in [231]. Last but not least, there is the group of socio-economically highly relevant psychiatric disorders, particularly major depression and schizophrenia, which have both been linked to abnormal retinoid signaling [232]. Several of the RXR-mediated mechanisms associated with mental/psychiatric disorders may be considered "disease-spanning", including neuro-inflammation, general inflamm-aging, synaptic plasticity, dopamine signaling, myelination/re-myelination, phagocytosis/brain-cleanup, homeostatic maintenance mechanisms within the central nervous system [204].

In **Alzheimer's Disease (AD),** RXR-mediated pathophysiological pathways include neuroinflammatory processes with microglial activation [233, 234], altered lipid homeostasis, particularly involving ApoE that is produced by astrocytes and microglia and affected by inflammatory activation of the latter. Moreover, the balance between the synthesis of amyloidogenic and non-amyloidogenic variants of amyloid-β peptides has been demonstrated to be under the control of retinoid signaling [235, 236]. Finally, RXR-agonists have been demonstrated to directly impact ApoE synthesis, restoring cognitive function in an AD mouse-model [237]. Altered retinoid-mediated ApoE synthesis in human macrophages upon inflammatory activation may represent an important link between RXR-mediated signaling, inflammation, ApoE homeostasis and AD [238]. In addition, in AD, abnormal myelin repair and demyelination are important dysfunctions [239] associated with dysfunctional RXR-mediated signaling [120, 240], which have been found to be associated with ApoE AD-risk alleles [241], and it was suggested that promyelinating strategies may ameliorate AD pathology and cognitive decline (reviewed in [242]). Even dopamine levels, dopamine receptors and dopamine signaling are reduced, as summarised in a systematic review [243], indicating there are multiple dysfunctions present in AD [244].

In Parkinson's disease (PD), where the degeneration of midbrain dopaminergic neurons represents a pathophysiological hallmark, retinoid- and particularly RXR-mediated signaling plays a pivotal role at numerous levels: At the level of retinoid synthesis, midbrain dopaminergic neurons highly express aldehyde dehydrogenases (ALDH1A), enzymes involved in both, dopamine and retinoid metabolism. At the level of RXR-mediated signaling, these neurons also characteristically express Nurr1/NR4A2, a heterodimeric binding partner to RXRs that has been found to be involved in the pathogenesis of PD [245, 246]. Therapeutic approaches, like BRF110, targeting heterodimers between Nurr1/NR4A2 and RXRα have been identified as neuroprotective agents in the preclinical setting [219]. Various

dysfunctions are present in PD including demyelination [247, 248] and altered dopamine, dopamine receptor levels and signaling [249, 250, 251].

Multiple sclerosis (MS), despite being recognized as an autoimmune disorder, involves both immune dysregulation and other aspects of (secondary) neurodegeneration that results in demyelination. Involvement of RXR-mediated signaling in both immunomodulatory and neuroprotective mechanisms is clearly evident and the efficacy of immunomodulatory treatments like bexaroten have been reported [252]. Treatments targeting RXR-mediated signaling have demonstrated efficacy in preclinical models with respect to enhancing re-myelination [253] and have recently entered clinical testing [254]. Moreover, minocycline, an antibiotic which can enhance local brain retinoid concentrations [233], has been demonstrated effective in the treatment of MS in independent clinical trials [255]. Also dopaminergic drugs are recently in discussion for treatment of selected MS symptoms [256], due to the fact that dopamine mediated signaling is altered in MS [257, 258].

In **schizophrenia** dysregulation of the dopaminergic neurotransmission has long been established as a hallmark of the disease, which is of particular relevance to retinoid signaling, as the key dopaminergic receptor (DRD2) is under the control of retinoic acid-response elements, thus directly regulated by RXR-signaling [229]. Besides dysfunctions in dopaminergic signaling myelination abnormalities were also reported in schizophrenia [259, 260], and may depend on abnormal RXR-signaling (as described above). Moreover, RXR-signaling has been found to regulate affective behaviour [203, 229, 261]. While early associative evidence [262] was recently confirmed at a genome-wide level [232, 263], one recent study confirmed a dysregulated retinoid homeostasis in schizophrenia patients and furthermore demonstrated pronounced involvement of retinoid signaling for one of the most important anti-psychotic drugs, supporting the strategy of a retinoid-based therapeutic approach [264]. Interestingly, RXR-directed therapeutic approaches using bexaroten have been pursued earlier with success [264, 265, 266, 267].

In **major depression disorder,** a pathophysiological relevance of retinoid signaling has long been established by epidemiological evidence from therapies interfering with cerebral retinoid homeostasis [268, 269]. More recent studies in post-stroke depression have demonstrated altered retinoid levels in patients and therapeutic efficacy of RXR-targeting strategies [270]. As already mentioned, RXR-mediated signaling has also been shown to modulate affective behaviour [203, 271]. Most importantly, retinoid signaling controls so-called meta-plasticity or homeostatic synaptic plasticity, which represents a well-defined type of synaptic plasticity that has also been termed "synaptic scaling" [272, 273, 274]. This process, which was most recently demonstrated to crucially involve retinoid homeostasis [275, 276], will likely also be affected by RXR agonists, as suggested by earlier reports on RAR – RXR-mediated plasticity [277, 278]. In major depression disorder also a severe dysfunction in myelination and the myelin content were observed [279, 280].

In summary, when comparing the individual pathophysiological background of these listed vitamin A5/X – RXR-signaling dependent diseases, then three major RXR-signaling dependent pathways are consistently present and likely to be "one of" or even "the" key relevant mechanisms of these multifactorial diseases. Indeed, as shown in Figure 4, these major pathways are dependent on RXR-mediated signaling and thereby the presence of sufficient endogenous RXR-ligand. Problems in a) myelination/re-myelination as well as b) dopamine signaling and c) phagocytosis/brain cleanup, neuro-protection and neuro-inflammation are known to be present in all five mentioned diseases. Focusing on one or even multiple vitamin A5/X – RXR-mediated pathways will offer valuable options not only to better understand pathogenesis of these complex multi-mechanistic diseases, but also offer targeted prevention and treatment options using nutritionally or/and pharmacological intervention strategies with selected vitamin A5/X-derivatives.

Indirect evidence and consequences of nervous system relevant RXR-mediated pathways

RXR exhibits a key role in nuclear receptor signaling by acting as universal heterodimeric partners for approximately one third of the nuclear receptor superfamily. While a few "non-permissive" RXR heterodimers (RXR – RAR, RXR – thyroid hormone receptor (TR) and RXR – VDR) require an agonist of the partner receptor for activation, several other "permissive" heterodimers can be activated by the sole binding of an RXR agonist. RXR ligands can therefore act through several heterodimers among which relevance for the nervous system [90] which has been demonstrated especially for the RXR – LXR, RXR – PPARγ and RXR – NR4A2 dimers.

Tailless homologue (TLX, NR2E1): In addition, dimerization of RXR with TLX has been observed *in vitro* [281, 282] which plays a critical role in neuronal health as regulator of neuronal stem cell homeostasis [283, 284]. Further studies are needed to evaluate the relevance of RXR – TLX dimerization and whether activation by RXR agonists can act through such dimer.

LXRs: The LXRs [285] are intracellular cholesterol sensors and endogenously activated by oxidized cholesterol

metabolites (so-called oxysterols) such as 24(*S*),25-epoxycholesterol and 24(*S*)-hydroxycholesterol [286, 287]. They control cholesterol homeostasis by regulating the expression of key genes involved in cholesterol transport and metabolism. LXR activation, for example, induces expression of the ATP-binding cassette transporters A1 (ABCA1 and ABCG1) and the apolipoproteins ApoE and ApoC. Both LXR subtypes LXRα (NR1H2) and LXRβ (NR1H3) form permissive heterodimers with RXRs and are found in the brain where they regulate central nervous system cholesterol homeostasis and have an anti-inflammatory role [287, 288]. Cholesterol is a key component of neuronal cell membranes and myelin sheaths, and thus highly important for the brain [79, 289, 290]. Central nervous system cholesterol mainly stems from de novo synthesis in astrocytes and transport to neurons, both of which are regulated by LXRs [287, 291]. LXR activation, for example, induces cholesterol efflux transporters ABCA1 and ABCG1 as well as ApoE for cholesterol transport to neurons [291, 292]. Lack of LXR, especially LXRβ, caused severe neuronal impairment with neuronal degeneration and thinner myelin sheaths as well as learning and motor deficits [215, 293, 294]. Moreover, LXR activation has anti-inflammatory effects in microglial cells, in particular by reducing cyclooxygenase 2 (COX-2) and inducible NO-synthase (iNOS) expression and NFκB activity [295, 296]. LXR-signaling is hence essential for neuronal health and RXR agonists might contribute to these aspacts through RXR – LXR dimer activation.

In addition to cholesterol homeostasis and anti-inflammatory activity, LXR-dependent mechanisms are speculated to have beneficial effects in neurodegenerative diseases. In AD, there is evidence for an involvement of LXR signaling in Aβ elimination/clearance [297, 298] and a strong connection appears from the ApoE epsilon-4 allele, which is a risk factor for the disease [299]. ApoE, whose expression is regulated by LXR, mediates brain cholesterol transport. The protein is therefore highly abundant in the CNS and was found to associate with Aβ plaques suggesting a potential protective role [299, 300, 301]. Interestingly, LXRα or LXRβ knockout in transgenic APP/PS1 mice (a mouse model for AD), led to an increased Aβ plaque burden [296]. In multiple sclerosis, LXR activity is thought to contribute to beneficial effects by promoting anti-inflammatory effects in microglia [302] and by controlling homeostasis of cholesterol – a critical component of myelin sheaths – in myelinating oligodendrocytes [303]. In addition to providing cholesterol for re-myelination, LXR seems to be involved in regulating phagocytosis of myelin and cell debris after demyelination and the subsequent switch to an anti-inflammatory remyelinating phase [302]. Moreover, it was found that LXR activation enhanced, while LXR knockout reduced, expression of myelin basic protein and proteolipid protein, as two major compounds of myelin [215]. LXRs and the RXR-LXR dimers thus hold therapeutic potential in neurodegeneration.

PPARs: Similar to LXR, the PPARs are activated by fatty acid and lipid metabolites [304, 305, 306, 307, 308]. They are crucially involved in the regulation of adipose tissue differentiation [309], glucose and lipid metabolism and in inflammation. All three PPAR isotypes are expressed in the brain [310], but a role in neuronal health is especially speculated for PPARγ. Evidence for a neuroprotective potential of PPARγ arises from the observation that treatment with glitazones reduced the risk to develop dementia [311, 312, 313] and PD [314]. Moreover, elevated PPARγ levels were detected in the cerebrospinal fluid of multiple sclerosis patients [315] while PPARγ expression in macrophages was diminished [316]. In the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, PPARγ agonist treatment ameliorated the disease [317, 318] and synergized with RXR agonist treatment [320]. The beneficial effects of PPARγ in neurodegenerative diseases are mechanistically referred to as mitochondrial protection, enhanced oligodendrocyte differentiation, anti-inflammatory effects, enhanced phagocytic activity of macrophages and microglia, improved clearance of myelin debris and modulation of T-cell differentiation [91, 318, 319, 322, 323, 324, 325, 326, 327]. In dementia and related diseases, PPARγ activation is additionally hypothesized to reduce Aβ and tau burden [91, 319] by induction of insulin-degrading enzyme, which can also degrade Aβ [328, 329] and downregulation of β-secretase expression which is involved in the formation of Aβ from amyloid precursor protein (APP) [329, 330, 331]. Although the neuroprotective effects have mainly been demonstrated with PPARγ agonists, the fact that PPARγ forms an obligate RXR heterodimer supports the assumption that RXR agonists can act through the permissive RXR – PPARγ heterodimer to exhibit beneficial effects on neuronal health.

NR4A2: A strong neuroprotective role is also ascribed to Nurr1/NR4A2 which can act as monomer and homodimer but also as heterodimer with RXRs [332, 333, 334]. It is a member of the nerve growth factor-induced clone B (NGFI-B) [335] subfamily (NR4A) of nuclear hormone receptors for which endogenous ligands remain elusive. NR4A2 lacks the canonical ligand-binding site of nuclear receptors [336] but can be modulated through other regions of the ligand-binding domain with small molecules [337, 338, 339, 340, 341]. It is mainly expressed in the central nervous system [342], where it regulates dopaminergic neuron development and survival [245] as well as inflammatory processes [343, 344]. Neuroprotective potential of NR4A2 is supported by several observations from animal models and human patients. Decreased neuronal levels of NR4A2 (knockdown or heterozygous knockout) in mice caused a

phenotype with features of PD [345] and worsened the pathology of AD models [346] and experimental autoimmune encephalomyelitis [347]. Furthermore, diminished levels of NR4A2 were detected in rodent models of PD [348, 349] and AD [350], and in human patients [351, 352]. Preliminary data also suggest that pharmacological NR4A2 activation counteracts neurodegenerative pathologies [341, 346, 353] although high-quality chemical tools for modulating NR4A2 activity are not available yet. The lack of potent and selective NR4A2 modulators and the fact that NR4A2 forms a permissive heterodimer with RXR has inspired the development of RXR – NR4A2 dimer-selective RXR agonists such as BRF110 [219] and IRX4204 [220], which have been shown to exhibit neuroprotective activity *in vitro* and *in vivo*. These findings support potential neuroprotection by RXR-agonists in the central nervous system via activation of the RXR – NR4A2 heterodimer.

In summary, vitamin A5/X can influence via RXR-activation and in addition to ligands of partner nuclear hormone receptors many pathways with impact on mental health, healthy brain aging and the prevention of neurological diseases and thereby vitamin A5/X may serve as a master switch enabling these response pathways [98, 102, 198].

Nutrition and RXR-mediated signaling; the prediction of a primary vitamin A5/X deficiency

Key processes that are both RXR-mediated and found to be dysregulated in neurological disorders include cholesterol metabolism, systemic immune-mediated mechanisms, general neuro-protection, phagocytosis/brain cleanup, Aβ-clearance, myelination/re-myelination, homeostatic synaptic plasticity and dopamine signaling (Figure 4). Here, we propose that **a primary vitamin A5/X deficiency**, defined by a non-sufficient nutritional supply of vitamin A5/X / provitamin A5/X, which is present mainly in fruits and vegetables [198] and postulated via a logical step by step cascade might contribute to the large prevalence of neurological disorders in the Western society [354).

These neurological disorders represent a growing socioeconomic burden and are expected to become one of the leading causes of disability worldwide along with the projected demographical changes [354, 355]. Current commercial data from the pharma-industry confirms the importance of neurological diseases while a large share of all pharma sales in the Western world relying on neuro-pharmaceuticals [354, 356].

A deficiency of nutritional supply is named a primary deficiency, in this case a **primary vitamin A5/X deficiency** (Figure 5). These primary vitamin deficiencies can easily be prevented by simply adding food components rich in these specific vitamins to our daily food.

Provitamin A5/X is present, like many other carotenoids, in various vegetables with a focus on leafy and root vegetables [198]. A larger range of fruits and vegetables was until now not analysed and is under investigation. Studies will focus especially on processed fruits and vegetables and products containing them, as thermal food processing was associated with induced isomerisation of all-*trans*-β,β-carotene/provitamin A(1) towards 9-*cis*-β,β-carotene/provitamin A5/X [357, 358, 359]. Regarding animal-derived food products screening will focus on meat and meat products from various nutritional relevant species, and animal-derived food products like eggs, milk and dairy products [99]. In addition, a large array of seafood products from fishes, crustaceans and others, which life are based directly or indirectly on a plankton/algae-based diet [360], are under screening. The Dunaliella algae strains [361], are known to be very high in 9-*cis*-β,β-carotene/provitamin A5/X [198, 362]. Whether these algae have a broader nutritional relevance for aquatic and terrestrial animals is questionable because especially this carotenoid, 9-*cis*-β,β-carotene/provitamin A5/X, accumulations depends on stress exposure [361, 363], these algae are naturally limited to high saline environment and are present in very restricted territories world-wide [364].

Polymorphisms in genes of the RXR-signaling pathways as a secondary vitamin A5/X deficiency

Besides nutritional intake as the cause of a primary vitamin A5/X deficiency genetic polymorphism in the genes of the RXR-signalling cascade are causes of a secondary vitamin A5/X deficiency (Figures 5 and 6). To dissect RXR-mediated signaling a large overlap between RAR – RXR-mediated signaling mediated by the endogenous RAR-ligand ATRA as well as by the endogenous RXR-ligand 9CDHRA must be dissected and evaluated [102]. A large overlap in nutrikinetics for both ligands is likely given for synthesizing metabolic enzymes like beta-carotene-oxygenase 1 (BCO1) and retinaldehyde dehydrogenases (ALDH1A1/2), retinoid binding proteins like retinol binding protein 4 (RBP4) and the cellular retinoic acid binding proteins (CRABP1/2) in addition to the RARs, which are mainly associated to ATRA – RAR-mediated signaling [103, 365]. Due to the high similarity in their chemical structure of 9CDHRA and ATRA, it is highly likely that these enzymes and binding-proteins are also involved in the regulation and control of ligand-regulated 9CDHRA – RXR – "alternative NHR" -mediated signaling.

Retinol binding protein 1 (RBP1) seems to be more specific for 9CDHRA – RXR – "alternative NHR"-mediated

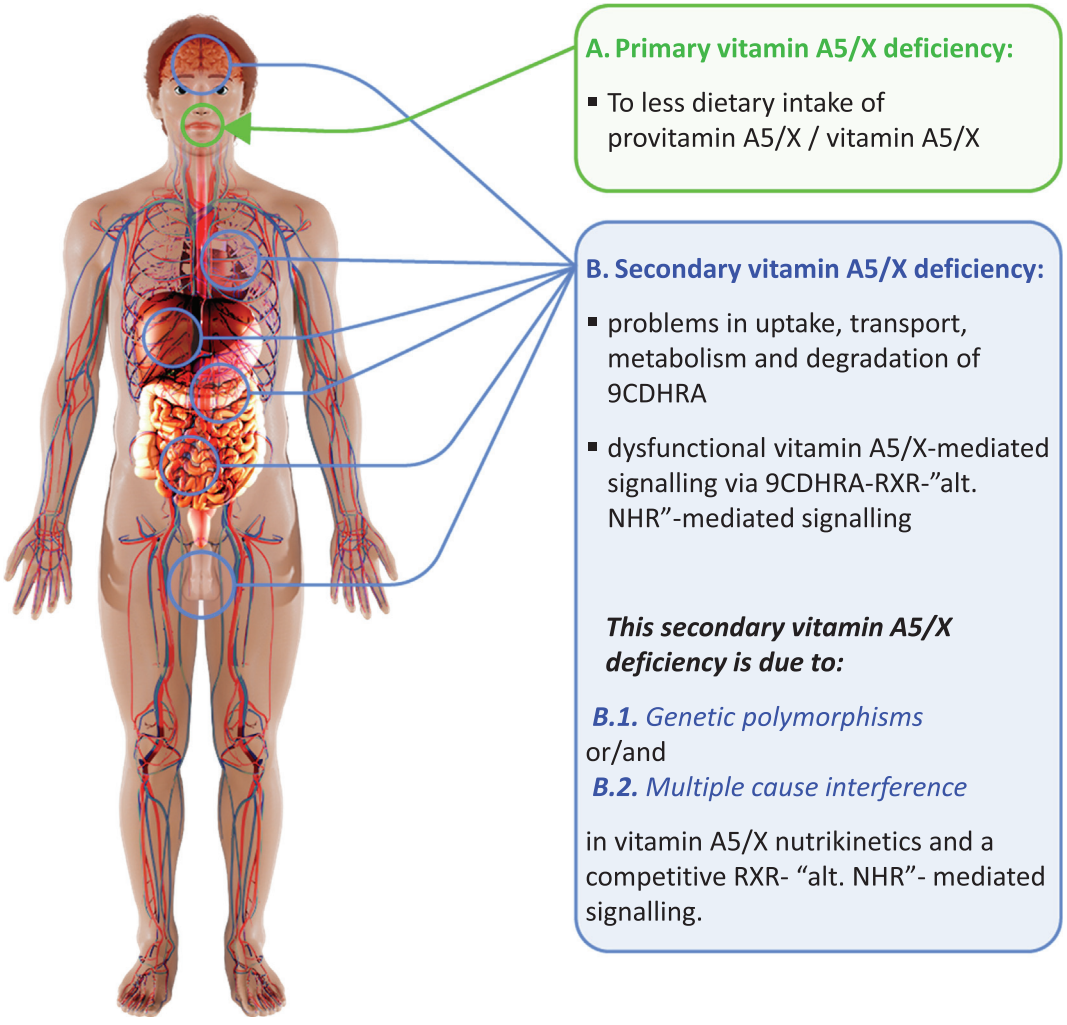

Figure 5. Summarized figure of mechanisms leading to a primary and secondary vitamin A5/X deficiency. *Abbreviations:* 9CDHRA: 9-*cis*-13,14-dihydroretinoic acid; RXR: retinoid X receptor; NHR: nuclear hormone receptor; alt: alternative.

signaling while an involvement of RBP1 in RAR - RXR-mediated signalling is also given [98, 100, 366]. In consequence, by controlling 9CDHRA production, RBP1 is thereby also involved in the individual alternative NHR - RXR-mediated signalling like for the RXRs, the LXRs, the PPARs, the VDR and the NR4A2 for 9CDHRA – RXR - "alternative NHR"-mediated signalling [98, 102, 198].

For all of these gene polymorphisms, it is known, which have a local [261, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388] or systemic [378, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 401, 402, 403, 404, 405, 406, 407, 408] relevance for prevention of nervous system diseases and drug addiction as well as for general healthy aging and optimal mental health (Figure 6).

When evaluating these polymorphisms present in humans then individual nutritional strategies are possibly relevant for an individual, to be tested for its genetic background and the possible cause of a **secondary vitamin A5/X deficiency**. Such secondary vitamin deficiency can be targeted with different pharmaceutical or nutritional strategies to ameliorate or even prevent these specific deficiency syndromes.

Is there a specific vitamin A5/X deficiency in humans?

Based on a general definition the term "vitamin deficiency" relates to two different kinds of scenarios; a) a deficiency based on too low intake of the vitamin defining thereby a **primary vitamin VA5/X deficiency** and b) a deficiency of uptake and further bioactivation as well as further processing of vitamin-mediated signaling, as a **secondary vitamin A5/X deficiency**, outlined in Figures 5 and 6. As the primary deficiency relates to a non-appropriate nutrition while the secondary deficiency related more to a

polymorphisms / targeted genetic modification (*) resulting in	● *local-dysfunctions / diseases*	● *systemic-dysfunctions / diseases*	
RAR - RXR-mediated			***ref.***
BCO1	-	● *obesity (*)*	*399*
		● *atherosclerosis*	*397*
RBP4	-	● *coronary artery disease*	*396*
		● *diabetes*	*400*
CRABP2	-	● *LDL homeostasis*	*398*
ALDH1A1/2	● *Parkinson´s*	● *blood pressure regulation*	374, 389
	● *schizophrenia*		*371*
	● *alcoholism*		*367*
	● *autism*		*377*
RARα/β/γ	-	● *immune response*	*403*
RAI1	● *depression*	-	*373*
RXR - "alt. NHR" -mediated			
RBP1	● *glioma*	-	*379*
RXRα/β/γ	● *schizophrenia*	● *lipodystrophy*	*261, 394*
	● *Alzheimer´s*	● *dyslipidaemia*	*393, 395, 368*
		● *diabetes*	*404*
		● *hypertension*	*401*
		● *hyperlipidaemia*	*401*
RXR-CoA	● *schizophrenia*	-	*370*
LXRα/β	● *Alzheimer´s*	● *lipid / glucose homeostasis*	*378, 391*
		● *obesity / diabetes*	*390*
PPARα/β/γ	● *Alzheimer´s*	● *diabetes*	*388, 402*
	● *glioma*	● *dyslipidaemia*	*376, 392*
	● *schizophrenia*		*261, 375*
VDR	● *Multiple sclerosis*	● *diabetes*	*380, 405*
	● *autism*	● *metabolic syndrome*	*381, 382, 406, 407*
	● *Parkinson´s*	● *hyperlipidaemia*	*383, 408*
	● *Alzheimer´s*		*384, 385*
	● *depression*		*386*
	● *cognitive-impairment*		*384, 387*
NR4A2	● *schizophrenia*	-	*261*

Figure 6. Gene mutations and polymorphisms occurring in indirect and direct brain and nervous system functions involved in RXR-mediated signaling pathways. *Abbreviations:* RXR: retinoid X receptor; NHR: nuclear hormone receptor; alt.: alternative; VDR: vitamin D receptor; RAR: retinoic acid receptor; LXR: liver X receptor; PPAR: peroxisome proliferator-activated receptor; NR4A2: nuclear receptor subfamily 4 group A member 2; BCO1: beta carotene oxygenase 1; RBP4: retinol binding protein 4; CRABP2: cellular retinoic acid binding protein 2; ALDH1A: aldehyde dehydrogenase 1A; RBP1: retinol binding protein 1; RAI1: retinoic acid induced gene 1; CoA: coenzyme A.

disease/dysfunctional status or genetic variety, where vitamin-mediated signaling is dysfunctional.

Based on the current knowledge in RXR-mediated signaling the following medium-term effects on general mental health and well-being like mental stress, anxiety, nervousness, depression, general loss enjoyment of life, irritability, insecurity, dissatisfaction, listlessness, sleeping disorders, restlessness, cognitive decline, addictive behaviors to drugs and drug-like stimuli and an increased incidence of neurological diseases are likely dependent on physiological pathways directly or indirectly involving vitamin A5/X-signaling. Dysfunctional signaling within these pathways may be associated with a vitamin A5/X deficiency. In addition, abnormal expression of (and/or signaling by) RXRs or pathways directly regulated by RXRs can be observed in a number of neurological diseases like neurodevelopmental diseases [204] and psychiatric diseases [92] thereby including autism, attention deficient hyperactivity disorder (ADHD), mental/psychotic disorders like major depression disorder, drug addiction, alcoholism, schizophrenia and

bipolar disorder, or neurodegenerative diseases [93] like AD, PD, dementia, amyotrophic lateral sclerosis (ALS), Huntington's disease and demyelinating diseases like MS and Guillain-Barré syndrome. Such observation suggest, that abnormal RXR-mediated signaling including its modulation by vitamin A5/X might be involved in the physiopathology of these diseases and/or that modulation of vitamin A5/X and RXR-mediated signaling might be an efficient method to normalize or prevent at least some aspects of the physiopathology of these diseases and related symptoms. In summary, when evaluating and summarizing based on a step by step cascade then a primary medium-term/or long-term vitamin A5/X deficiency might in logical consequence result in non-optimal mental health/well-being, drug addiction, non-optimal brain-aging, as well as is a potential cause of listed neurological diseases (Figure 7).

As analytical monitoring of provitamin A5/X, vitamin A5/X and active derivatives of vitamin A5/X was just recently established for the human body and food examination it is difficult to associate specific neurological diseases with reduced vitamin A5/X levels in specific easy and more advanced accessible compartments of the organisms. In addition even more importantly reduced vitamin A5/X dietary intakes by specific food components enriched in vitamin A5/X of the daily ingested diet should be studied. However, as important specific functions were already outlined (Figure 4), it would not be surprising and thereby in consequence logical, that – due to low intake of vitamin A5/X and provitamin A5/X – potential deficiency syndromes occur.

Especially vegetables are high in vitamin A5/X [198] and therefor likely reduced intakes of vegetables are co-associated with compromised RXR – vitamin A5/X-signalling, thereby increasing the incidence not only of neurological and psychiatric conditions [409] and mental well-being [410], but also cardio-vascular diseases [411], cancer [412] and allergies [413]. A clear causal and proven step by step connection that reduced vegetable intake results in reduced endogenous vitamin A5/X-derivatives, reduced vitamin A5/X – RXR-mediated signaling and an increased incidence of specific diseases and other RXR-co-associated physiological dysfunctions resulting in non-optimal health and increased prevalence of specific diseases was until now not identified, but appears highly likely and is under current evaluation by us.

The logic approach of the vitamin A5/X concept; a step by step approach

The intake of sufficient vegetables and fruits is associated with low incidences of neurological diseases as major depression disorder, neurodegenerative diseases, demyelinating disorders [414, 415, 416, 417], reduced carving for drugs and drug-like stimuli [418], healthy brain aging [409, 419], a low incidence of cognitive disorder [420] as well as with a general good mental health [409, 419]. To selectively delete vitamin A5/X from the animal or human diet for further targeted evaluation of the effects of a selective vitamin A5/X deficiency is not possible, because fruits and vegetables are not just rich in carotenoids in addition to provitamin A5/X. Indeed, they also contain other carotenoids like lutein/zeaxanthin with beneficial brain-associated effects [421], but also many other food bioactives with beneficial health effects [422]. A clear connection of exclusively the provitamin A5/X content in vegetables with mental health based on RXR-mediated signaling is not possible to examine, while it seems partly logic and reasonable and worth to be studied in further details.

In addition, vitamin A5/X derivatives were synthetically synthesized [99, 100] and tested in relevant models for cognition, stress and anxiety [99, 100, 101]. In these experimental models, these substances selectively confirmed effects on stress and anxiety prevention and improving memory/cognitive functions [99, 100, 101], which can be observed from correlation-based studies with a diet high in vegetables and especially leafy and root vegetables [409, 414, 415, 417, 419]. Not surprisingly, vegetables and especially leafy vegetables are high in provitamin A5/X [198].

In summary, let us conclude that we identified an important food factor which originates from vegetables/leafy vegetables which is likely "one of" or "the" relevant food factor for a general mental health, a well-functioning central and peripheral nervous system, healthy brain aging, drug addiction potential and for the prevention of neurological diseases involving RXR-mediated signaling pathways depending on dietary intake of vitamin A5/X.

Proof of concept in translational clinical supplementation studies

Algae/microalgae extracts have been given not only to animal models [423, 424, 425, 426], but have also been tested and given to human volunteers [427, 428, 429]. These supplementations were targeting diseases where an RXR-mediated dysfunction was observed and this disease phenotype is based on dysfunctional immune responses as well as a dysfunctional lipids and glucose homeostasis [427]. Protection or even a partly reversal of an RXR-dependent phenotype was possible by Dunaliella algae supplementations [427] and associated with their vitamin A5/X – RXR-ligand – precursor function [99, 101]. The direct RXR – LXR target was HDL-cholesterol [430, 431], which was under control of RXR-ligand and serves as an

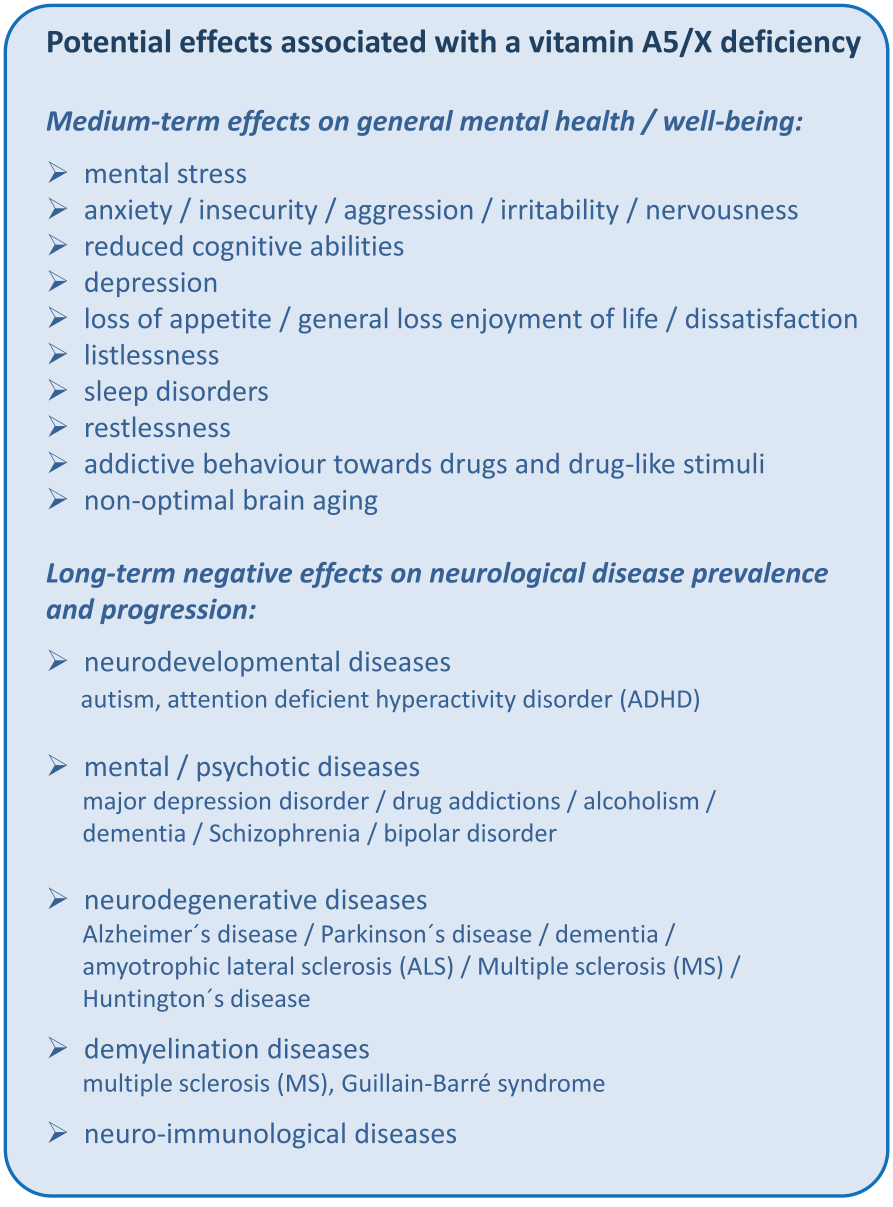

Figure 7. Summary: What are the potential effects of the step by step highlighted vitamin A5/X deficiency?

easy accessible marker of RXR-mediated signaling [100]. These clinical interventions clearly link vitamin A5/X / provitamin A5/X supplementations with improved RXR-mediated signaling in humans. Recently, a correlation of serum 9CDHRA levels, in physiological and non-pathophysiological conditions, with the RXR-target, IL4, as a marker of general Th2-immune response, was found in humans [167]. Interestingly, IL4 is also associated with critical functions in the normal brain, such as memory and learning [432].

Based on these clinical studies and chosen application dosages of the algae extracts given, which can easily be calculated as equivalent to vitamin A5/X-units, similar beneficial effects on further targets of RXR-mediated signaling for good mental health, drug addiction potential, healthy brain aging and for the prevention of neurological diseases can be logically foreseen and will deserve further investigation [98, 99].

What is urgently or prospectively missing in vitamin A5/X research?

Our recommendations for future research and actions taken by governmental authorities:

- What are the direct food sources of vitamin A5/X and provitamin A5/X? How much of these food sources do individual groups eat on a daily or monthly basis? Do we eat sufficient amounts of these food components to

have enough vitamin A5/X in our daily diet? Are these vitamin A5/X sources sufficient to maintain optimal RXR-mediated signaling for a good mental health?
- Are there population groups which eat less vitamins A5/X and which have a higher incidence of RXR-signaling dependent diseases or dysfunctions? Are these diseased persons or person like pregnant woman, elderly or children just dependent on a primary vitamin A5/X deficiency based on food intake or is a secondary vitamin A5/X deficiency being fully, additive or partly present?
- How can we detect such a vitamin A5/X deficiency? Which direct and indirect measures must be performed? Which biological matrix is needed to determine a vitamin A5/X deficiency? Would there be an easy option "to do" in daily doctor's life or even options to be performed by health-conscious individuals on a daily base?
- Are there crucial metabolic steps or selective food compounds which are vitamin A(1) - RAR - RXR-independent and specific for the vitamin A5/X-RXR signalling cascade to selectively examine a vitamin A5/X-selective vitamin A5/X deficiency in genetic manipulated animals of even in humans
- Are there preventive or even treatment-based supplementation options in development for people with a non-well mental health, drug addiction or even with mental diseases/neurological diseases as novel options in the food and pharma area?

Summary

A healthy balanced diet, rich in vegetables, especially root and leafy vegetables, is associated with a good mental health and well-functioning central and peripheral nervous system [10, 12, 13, 68]. Compounds present especially in these vegetables may contribute as key factors for medium-/long-term effects on mental well-being, healthy brain aging, drug addiction potential and for the prevention of neurological diseases.

While many nutrients were associated with a healthy well-performing brain, no clear "food – nutrient – signaling – clinically proven positive impact" was identified so far for any specific substance. Many dietary suggestions for mental health were summarised indicating to be rich in nutritional precursors for the nuclear hormone receptors mentioned in this article, while even leafy vegetables rich in RXR-ligand precursors are always included in these recommendations [433]. We now added vitamin A5/X and interaction of further signaling via the vitamin A5/X-receptors, the RXRs, as a new piece to this large puzzle as a food component and specific nutrient towards an optimal physiological/nutritional signaling concept.

Using a logical step by step cascade approach summarized in this review, we associate a low dietary intake of green vegetables, which are high in vitamin A5/X, like present in large parts of the Western society with non-optimal brain health and cognitive performance; this may represent a significant public health problem, which could – based on a logical step by step cascade – be easily corrected by advising higher dietary intakes of provitamin A5/X / vitamin A5/X via: a) natural food components, b) food fortification with natural based extracts rich in vitamin A5/X, or c) additional dietary supplementation of vitamin A5/X for medium-/long-term effects in improving and maintaining brain health, enabling healthy brain aging, prevention of drug addiction potential and prevention of high prevalence of common neurological diseases in the Western society.

Just recently, this new vitamin pathway, with direct and indirect influence on brain-/nervous-system functions, was found. Based on nutritional calculations this vitamin seems to be too low in the general Western diet [198]. A high daily dietary vegetable (especially green vegetables) intake of provitamin A5/X, optimal serum levels of provitamin A5/X / vitamin A5/X, further optimal vitamin A5/X receptor (RXR)-mediated signaling and further transcriptional regulation directly or indirectly are all of relevance for the brain based on current scientific evidence [104, 198, 421].

These facts are all proven on a step by step cascade in a comparable manner like established for most other vitamins, while the whole cascade starting from A) vegetable intake via B) systemic vitamin A5/X levels via C) local vitamin A5/X-receptor (RXR)-mediated signaling via D) alteration of gene transcriptional regulation of response ways in the brain and E) towards direct effects on good mental health and performance, a well-functioning central and peripheral nervous system, healthy brain aging as well as the prevention of drug addiction potential and neurological diseases have not been proven in human-based clinical studies, which is again comparable to most other vitamins.

Novel nutritional strategies and pharma-options based on the vitamin A5/X cluster derivatives aiming a maintenance or even additive/"plus"-activity for a good mental health and pharma options for treatment of neurological diseases are discussed and partly in current development.

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