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REVIEWS: CURRENT TOPICS

Involvement of omega-3 fatty acids in emotional responses and hyperactive symptoms☆

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Abstract

Biochemical evidence suggests a role for n-3 polyunsaturated fatty acids (n-3 PUFAs) in the regulation of behavioral disturbances. A number of studies have revealed an association between reduced n-3 PUFA levels and attention-deficit hyperactivity disorder or depression. Here, we summarize the main findings regarding the association between n-3 PUFA and hyperactive and emotional disorders, and discuss potential mechanisms of action. Because the basal ganglia are involved in the control of locomotion and emotion, we examined published data regarding the role of n-3 PUFA in dopamine (DA) regulation in the basal ganglia. These results are discussed in the light of recent data from our laboratory suggesting an association between the drop in melatonin in the pineal gland and the increase in DA in the striatum and nucleus accumbens of n-3 PUFA-deprived rodents.

Keywords: n-3 PUFA; Emotional response, Hyperactive symptoms, Rodents, Melatonin, Dopamine

1. Introduction

Over the past 10 years, numerous studies have investigated the benefits of dietary n-3 polyunsaturated fatty acids (PUFAs) for the brain. The interest stems from evidence that n-3 PUFAs play roles in brain structure and function and may reduce the development of various neurological disorders (reviewed in Ref. [1]). Indeed, a growing body of evidence suggests that perinatal accrual of n-3 PUFA in the brain may represent a neurodevelopmental protective factor for the subsequent emergence of psychopathology [2,3]. Although there is considerable heterogeneity in the results and marked variation in the study methodologies, increasing evidence implicates n-3 PUFA in the regulation of various disorders of mood and behavior [4]. Epidemiological, clinical and interventional studies have investigated the association between n-3 PUFA intake and inattention, hyperactivity and behavioral disorders [5,6], and some have revealed a notable association between reduced n-3 PUFA levels in red cell membranes and attention-deficit hyperactivity disorder or depression [7–9]. In this review, we explore data regarding the association between n-3 PUFA and behavioral functions obtained from studies using animals fed n-3 PUFA-deprived or -enriched diets. In order to elucidate the possible mechanisms involved, we focused on works that demonstrated the impact of n-3 PUFA in the basal ganglia, notably the striatum and nucleus accumbens, which is involved in the control of locomotion, affect, impulsivity, attention and emotion. Interactions between glutamate, GABA and dopamine (DA) in the basal ganglia have been suggested to be involved in the regulation of these functions [10–12], and the role of n-3 PUFA in dopaminergic neurotransmission is well documented [13]. We summarize the main findings and discuss these results in the light of our recent data suggesting an association between the drop in melatonin (MEL) in the pineal gland and the increase in DA in the striatum of n-3 PUFA-deprived hamsters.

2. n-3 PUFA and the brain

Second to adipose tissue, the central nervous system has the highest concentration of lipids in the body (30–50% of the dry weight of the brain). Long-chain polyunsaturated fatty acids (LC-PUFA), especially docosahexaenoic acid (DHA; 22:6 n-3) and arachidonic acid (AA; 20:4 n-6), are fundamental components of membrane phospholipids in neural cells. High levels of DHA, particularly in phosphatidylethanolamine (>20% and >40% of total fatty acids in the brain and retina, respectively), are characteristic of neural tissue. At the subcellular level, the highest concentrations are found in the membranes of synaptosomes and photoreceptor outer segments. DHA and AA can be obtained directly from the diet or be converted from their precursors, α-linolenic acid (ALA; 18:3 n-3) and linoleic acid (LA; 18:2 n-6), respectively (Fig. 1). As essential fatty acids, ALA and LA must be obtained from dietary sources because humans and most other mammals lack the ability to synthesize them. ALA and LA are mainly found in seeds and vegetable oils. After absorption, these two fatty acids lead, *via* the same metabolic conversion pathway, to

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the specific synthesis of AA for the n-6 series and of eicosapentaenoic acid (EPA; 20:5 n-3) and DHA for the n-3 series (Fig. 1). DHA levels in neural membranes vary according to dietary n-3 PUFA intake. Because the conversion of ALA to DHA competes with the conversion of LA to AA, the LA/ALA ratio is a major nutritional parameter for DHA accretion.

To evaluate the role of dietary n-3 PUFAs in physiological and behavioral disturbances, most experimental studies induce severe DHA depletion by multigenerational dietary n-3 PUFA deprivation. The deficiency is induced using experimental diets in which dietary lipids are vegetable oils containing a very low amount of ALA (with no DHA) and some amount of LA to inhibit the conversion of residual ALA to DHA. Such dietary manipulation reduces the amount of DHA in membranes and increases that of n-6 PUFA, AA and mainly docosapentaenoic acid (DPA; 22:5 n-6), leading to an n-6/n-3 imbalance in the brain [14]. The balance between AA and DHA is a major determinant in the maturation of brain function [15] and appears crucial for brain development, particularly at the time of neuronal migration, myelination, neurite growth and synaptogenesis [16]. It has been shown in rodents and nonhuman primates that inadequate supplies of n-3 PUFA during the perinatal period result in impaired learning capacity, neurotransmission processes and visual function [1,13,17].

3. In Western countries, dietary n-3 PUFA intake from early life until adolescence is generally not sufficient to support optimal neuronal functioning

Results from studies of human nutrition have raised the questions of which and how much of the different n-3 PUFAs are needed in the diet and whether the current intakes high in n-6 and low in n-3 PUFA contribute to impaired neural development and function.

Adequate intake of n-3 PUFA, balanced with that of n-6 PUFA, is crucial for optimal accretion of DHA in the brain. The n-3 PUFA intake depends on both ALA and DHA itself because humans have a low capacity for converting ALA to DHA (<0.5%) [18]. Adequate ALA intake in healthy adults is 0.7–1% of energy intake with an LA/ALA ratio ranging from 5 to 10 [18,19]. A DHA intake of 250–300 mg/day is also recommended, which is particularly crucial for pregnant and lactating women in terms of brain development benefits for the fetus (*via* placental transfer from mother's circulation) and the newborn infant (*via* breast milk) [20]. However, 30–80% of Western populations have ALA and/or DHA intakes below these recommendations [19,21–23]. Generally associated with high LA intakes, an imbalance in the LA/ALA ratio (>15) reduces the DHA availability for brain metabolism in humans.

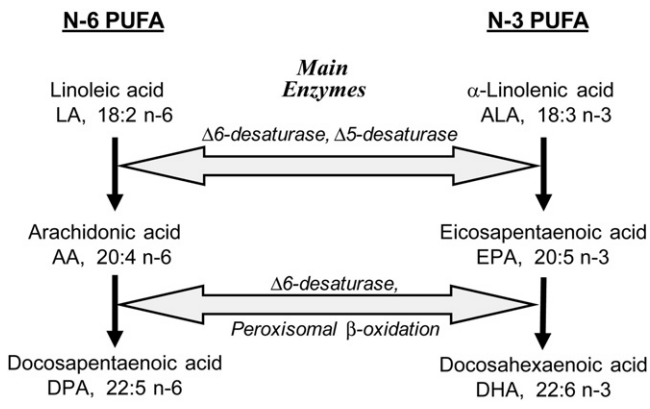

Fig. 1. Metabolism of n-6 and n-3 polyunsaturated fatty acids (PUFAs). The essential fatty acids linoleic acid (LA) and a-linolenic acid (ALA) are the metabolic precursors of n-6 and n-3 PUFAs, respectively. Once obtained from the diet, these two PUFAs are converted by the same successive desaturation (Δ-6 and Δ-5 desaturation) and elongation steps to arachidonic (AA) and eicosapentaenoic (EPA). EPA can be further metabolized to DHA by Δ-6 desaturation and peroxisomal b-oxidation. In response to dietary n-3 PUFA deficiency, AA is partly converted to docosapentaenoic acid (DPA) to substitute for DHA in membrane phospholipids.

Several studies have evaluated the effects of imbalanced consumption of n-6 and n-3 PUFAs during the perinatal period (for review see Ref. [19]). In Canadian pregnant women, insufficient DHA (110 mg/day) and excessive LA consumption were suggested to contribute to suboptimal visual acuities in 2-month-old infants [20]. In lactating women, PUFA content in breast milk is a reliable marker of long-term PUFA consumption and corroborates with data obtained from food consumption surveys [19]. Disequilibrium between n-6 and n-3 PUFA mainly results from high LA, low ALA and/or low DHA consumption, and varies geographically (*i.e.*, high LA and low DHA in the US; low DHA in Canada; very low ALA in Southern Europe). In France, the mean content of ALA in women's breast milk is about 0.6% of total fatty acids, whereas the minimum recommended value in infant formulas is 1% of total fatty acids [24]. Indeed, 30% of the French women in this study had a 30–40% increase in their LA/ALA ratios in breast milk following persistent high consumption of LA throughout the course of lactation. Dietary intake of LA has increased progressively in Western countries during the last few decades [19].

The recommended daily intake of ALA for children and adolescents is the same as that recommended for the general population (1% of energy intake) [19,25]. The recommended daily intake of DHA for adolescents is 250 mg/day and that for children is 125 mg/day [26]. The few available consumption surveys from Western countries indicate inadequate intakes of n-3 PUFA [25–30]. Sioen et al. [25,26,31] conducted a longitudinal evaluation in a specific population in Belgium that showed the impact of family dietary habits on n-3 PUFA intake. Low ALA consumption in adult women (0.57% energy) was mirrored in their young (between 2.5 and 6.5 years of age) and adolescent children. Dietary DHA deficits evident in adults (131 mg/day) were more pronounced in their adolescent children (111 mg/day). More than one-third of the studied adolescents did not consume any seafood. Thus, the n-6/n-3 PUFA disequilibrium observed in adults was accentuated in adolescents, which limits DHA biodisponibility for their brains. Interestingly, a number of studies have reported a lower n-3 PUFA blood status in children and adolescents affected by attention-deficit hyperactive disorder (ADHD) [32].

4. Hyperactive symptoms and n-3 PUFA studies

In experimental animal models of ADHD, locomotor hyperactivity is usually the main outcome measured. Increased locomotor activity in rodents is often associated with elevated dopaminergic tone. It can be induced by different genetic or pharmacologic manipulations of the DA system [33,34]. Data from several studies highlight the importance of dietary n-3 PUFA intake in the appearance of these symptoms.

4.1. Human studies

ADHD is a common neurodevelopmental disorder characterized by inappropriate levels of hyperactivity, impulsivity and inattention. However, the etiology of ADHD is complex and associated with both genetic and environmental factors. From the first report describing signs of fatty acid deficiency in hyperactive children [35], a number of observational and epidemiological studies and intervention trials have investigated the relationship between n-3 PUFA deficiency and ADHD symptoms. Consensus among studies is difficult due to the variety of disorders and the use of different biological samples to determine the n-3 PUFA status (plasma, erythrocyte membranes,

adipose tissue). Thus, data from the human studies on the role of n-3 PUFA in the regulation of ADHD disorder are limited [5,6,36,37].

4.2. Animal studies

Numerous investigators have evaluated the effect of n-3 PUFA on motor activity in rodents (for review see Ref. [4]). Several have reported an increase in locomotion in n-3 PUFA-deficient rodents. Basal locomotor activity in a novel environment, videotaped for 2 h [38], moving time measured in individual cage for 20 min [39] and turns counted overnight (12 h) in rats placed in cylindrical rotometers [40], was significantly higher in n-3 PUFA-deficient rats than in control rats. In addition, in the last cited study, we demonstrated that behavioral lateralization was abolished in n-3 PUFA-deficient rats.

Spontaneous locomotor activity recorded over 48 h showed that n-3 PUFA-deficient mice were much more active than those fed an n-3 PUFA-enriched diet (containing perilla oil) during the dark and the light phases [41]. In our laboratory, measuring voluntary wheel running activity recorded for several weeks revealed that n-3 PUFA-deficient hamsters exhibited an 85% increase in the number of wheel revolutions during the light phase and a 68% increase during the dark phase as compared to controls. The time spent in the wheel was also increased by 1 h during the night (Fig. 2). These alterations evidenced that an n-3 PUFA-deficient diet induced long-lasting hyperactive locomotion independent of stress or exploratory behavior [42].

Interestingly, in mice maternal exposure to a diet high in n-6 fatty acids during pregnancy (which reduced n-3 PUFA content in membrane phospholipids) augmented locomotor activity in the offspring [43]. Likewise, spontaneously hypertensive rats exhibit locomotor hyperactive symptoms and low DHA in their plasma and brain membranes [44,45]. In line with these results, we have shown that impulsiveness and high locomotor responses to novelty were associated with low DHA levels in rats fed a normal diet [46]. Although some studies found no influence of reduced dietary n-3 PUFA intake on locomotion, all these observations are consistent with the potential involvement of altered brain DHA content in the manifestation of hyperactive symptoms.

5. Emotional response and n-3 PUFA

Whereas dietary n-3 PUFA deficit-induced disturbance of locomotor activity has been well described [4], few data are available concerning the specific effects on emotional response.

5.1. Human studies

In humans, the administration of fish oil rich in DHA was shown to improve resistance to the mental stress of exams in students [47] and to blunt the associated increase in stress markers (plasma epinephrine, cortisol, energy expenditure) after 30 min of induced mental stress in young men [48]. Moreover, prevention of stress-induced aggression and hostility by DHA supplementation has been demonstrated in clinical trials [49,50].

5.2. Animal studies

DHA appears to be involved in the regulation of stress response in rats because DHA supplementation completely reversed the anxiety-like behavior induced by an n-3 PUFA-deficient diet and attenuated the freezing behavior in conditioned-fear stress responses [51]. Fedorova et al. [4] showed that n-3 PUFA deficiency differently affected anxiety levels in mice maintained under normal or stressful conditions. Deficient mice displayed a higher level of anxiety in response to stress than did the control group, whereas no significant difference was observed under low stress conditions.

In our laboratory, we have evaluated the effects of n-3 PUFA supplementation in mice submitted to unpredictable chronic mild stress (UCMS) for 8 weeks. As expected, repeated exposure to mild stressors resulted in deterioration in the physical state of the coat and decreased weight gain. A clear effect of UCMS was also observed in the resident–intruder test in which the decrease in latency to attack of the intruder confirmed the increased level of aggressiveness in stressed animals. n-3 PUFA supplementation, associated with increased incorporation of DHA in brain membrane phospholipids, was lesser in the stressed animals [52] than in controls. Despite n-3 PUFA supplementation, stressed animals exhibited no change in the level of aggressiveness.

Chronic stress and depression-like symptoms can be modeled in rats. Early maternal separation (MS) induced by disrupting normal maternal–infant interaction mimics the effects of early life neglect by parents in human infants and is considered to be one of the most powerful stressors for rats. Therefore, the MS paradigm constitutes a valid environmental model for early life stress and development of a depression-like syndrome in rats [53]. Using this paradigm, we recently showed that separated rats maintained under chronic dietary n-3 PUFA deficiency exhibited behavioral impulsivity and changes in the reward response in adulthood [54]. We demonstrated that the n-3 PUFA-deficient status and the MS stress acted synergistically to increase sucrose consumption used as marker of stress. Furthermore,

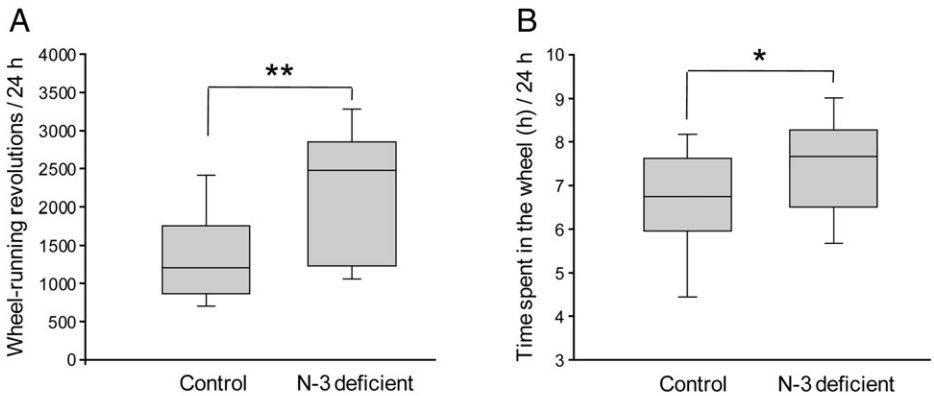

Fig. 2. Effect of n-3 polyunsaturated fatty acid (PUFA) deficiency on locomotor activity in Syrian hamsters recorded over the light/dark cycle for 30 days [42]. Values are expressed as means of the number (median±Q1, Q3) of wheel running revolutions (A) and hours spent in the wheel (B) over the light/dark cycle. *P=.017 and **P<.001 as compared to control animals (Mann–Whitney test); n=26.

n-3 PUFA-deficient rats showed increased reactivity to novelty in the open field test as expressed by a decline in latency to move and an increase in locomotor activity as compared to control rats. In parallel, we observed that loss of DHA in neural cell membranes was compensated for by an increase in n-6 PUFA, especially AA, and this was particularly pronounced in rats subjected to MS. Moreover, we demonstrated that the n-3 PUFA deficit associated with MS increased the reactions of conditioned fear and anxiety when rats coped with an inescapable stressful situation (unpublished data). In addition, the reaction of fear persisted longer and was restored earlier after a phase of extinction in the n-3 PUFA-deficient animals.

These observations suggest that a chronic deficit in n-3 PUFA increases vulnerability to mood disorders induced by chronic stress and that an adequate supply of n-3 PUFA could help to promote adequate coping mechanisms in response to stressful situations.

6. Proposed mechanisms

6.1. n-3 PUFA and dopaminergic neurotransmission in the basal ganglia

Frontostriatal circuitry that connects the frontal cortex to the basal ganglia is a prominent pathway involved in the control of locomotion, affect, impulsivity and emotion. The interactions between glutamate, DA and GABA in the basal ganglia have been suggested to be involved in the regulation of these functions [10–12]. Although the nature of these reciprocal interactions is not yet well understood, dysfunction of these interactions has been shown to be involved in several neurological disorders. The role of n-3 PUFA in regulating neurotransmission has been studied mostly in mesocorticolimbic monoaminergic systems. It has been shown that dietary-induced deficits in brain DHA accrual lead to abnormalities in DA neurotransmission in the adult rat brain (reviewed in Ref. [13]). Review of these studies suggested that the results depended on the experimental protocols, specifically whether DA levels were measured under physiological conditions or in response to pharmacological stimulations. To assess a correlation between hyperactive and emotional behaviors and DA dysregulation in n-3 PUFA-deficient rodents, we considered only those results obtained under basal conditions where basal DA levels were measured in samples from either extracellular space (by microdialysis) or brain tissues (endogenous content).

Both the basal extracellular level and the endogenous DA content measured in the shell part of the nucleus accumbens of rats [55] and in the striatum of hamsters [42], respectively, were significantly greater in n-3 PUFA-deficient animals than in controls. Interestingly, a similar increase in basal DA levels was reported in adult mice receiving an n-3 PUFA-deficient diet for 80 days [56]. Conversely, rats fed an n-3 PUFA-enriched diet (fish oil) exhibited a lower DA level in the striatum as compared to the control group [57]. Moreover, the striatum content of DA metabolites [3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA)] was increased in n-3 PUFA-deficient hamsters and mice [42,56], indicating activation of DA metabolism and increased DA utilization in the striatum. The striatal hyperdopaminergia that we observed in n-3 PUFA-deficient rodents is consistent with the observed hyperactive locomotion and enhanced responsiveness to stress.

This striatal hyperdopaminergia could result from disturbances at different levels of dopaminergic regulation. DA transmission is controlled not only by processes governing DA release, but also by regulation of extracellular DA concentrations *via* rapid reuptake by the plasma membrane DA transporter DAT. Moreover, autoreceptors (D2, D3 and D4 members of the D2 receptor subfamily) expressed at nerve terminals of DA neurons modulate DA synthesis and release. Several studies have demonstrated the relationship between receptors and transporters, DA levels, and locomotor activity. D2 receptor-deficient mice showed reduced wheel-running activity [58] without changes in basal extracellular striatal DA levels [59]. In contrast, D3R-mutant mice exhibited a hyperactive phenotype associated with a higher basal extracellular level of DA [60–62] and elevated DA uptake by striatal synaptosomes [63]. Thus, D2R and D3R have distinct roles in the control of basal extracellular DA levels. On the other hand, inactivation of DAT also produced spontaneous hyperlocomotion by prolonging the presence of DA in the extracellular space [33].

Therefore, disturbances in membrane receptors and/or transporters could explain the high endogenous and extracellular levels of DA in the striatum and nucleus accumbens of n-3 PUFA-deficient rodents. Indeed, dietary n-3 PUFA deficiency induces biophysical alterations of the brain cell membranes characterized by an unbalanced AA/DHA ratio. These changes affect the activity of membrane-bound proteins, including enzymes, receptors and transporters [64,65]. Modifications in DA receptors, namely, increases in D2 receptors (D2R) in the nucleus accumbens [55,66], have been observed in n-3 PUFA-deficient animals. These findings suggest that the data obtained from n-3 PUFA-deficient animals are not complete enough to allow meaningful interpretations, as the specific distribution of D2R and D3R in the striatum and in the shell of the nucleus accumbens, respectively [67], and their distinct roles have not been taken into account.

Furthermore, no changes in the DAT in the striatum [68,69] or nucleus accumbens [55] of n-3 PUFA-deficient rats were shown. However, the loss of lateralization associated with hyperactive locomotion that we observed in n-3 PUFA-deficient rats [40] has also been described in DAT-knockout mice exhibiting hyperdopaminergia [70].

6.2. n-3 PUFA and melatonin

Melatonin is a neurohormone of the pineal gland that is secreted rhythmically, with high levels occurring at night. In addition, the pineal gland can convert PUFAs into bioactive lipid mediators, some of which regulate MEL release.

An early study reported a significant decrease in MEL release in cultured pineal glands from rats raised on n-3 PUFA-deficient diet [71]. Thereafter, Zaouali-Ajina et al. [72] described a 32% reduction in 6-sulfatoxymelatonin, the main MEL urinary metabolite, collected over the nighttime from n-3 PUFA-deficient rats. We recently showed that, in hamsters, the elevated AA/DHA ratio in brain membranes resulting from n-3 deficiency was particularly high in the pineal gland (eightfold increase over controls) as compared to other brain structures (threefold increase in the cortex and twofold in the striatum). In these hamsters, the pineal MEL content declined by 52% during the night, resulting in the dampening of the MEL rhythm [42]. In addition, it has been demonstrated that endogenous 12-hydroxyeicosatetraenoic acid (12 HETE, produced by 12-lipoxygenase metabolism of AA), which stimulates MEL release [73], was decreased by 35% in the pineal glands of n-3 PUFA-deficient rats [74]. These data indicate that pineal gland function is specifically altered by n-3 PUFA deficiency.

Recent work from our laboratory [42] showed that altering MEL function in n-3 PUFA-deficient hamsters weakens the endogenous rhythm of the circadian clock and may play a role in sleep disturbances [75], as described in children with ADHD [76]. Interestingly, patients with autistic disorder exhibit low plasma DHA levels [77] and abnormally low mean excretion of 6-sulphatoxymelatonin related to abnormalities in MEL physiology and dysregulation of circadian rhythms [78]. Therefore, some of the hyperactive symptoms observed in n-3 PUFA-deficient animals and in hyperactive disorders in humans could be due, at least in part, to the impact of the n-3 PUFA deficit on pineal function and circadian rhythms.

6.3. Melatonin/dopamine interactions in the striatum

Several lines of evidence clearly implicate MEL in the regulation of dopaminergic pathways (for review see Ref. [79]). Alexiuk and Vriend [80] showed that daily subcutaneous injections of MEL inhibited dopaminergic activity in the medio-basal hypothalamus in Syrian hamsters. The authors also reported that after 5 weeks of MEL treatment, posterior pituitary DA content was reduced to less than 50% of that in control animals [81]. Perfusion of 500 μM MEL into the neostriatum of Wistar rats for 19 h decreased DOPAC and HVA levels by 75% and 79%, respectively, during the light phase [82]. MEL interaction with striatal DA was also demonstrated in C57BL/6 mice. Pinealectomy blunted the rhythm of DA and DOPAC, and evening intraperitoneal injections of MEL for 6 days restored the rhythm, showing a dose-dependent effect on DA/DOPAC turnover [83]. In n-3 PUFA-deficient hamsters in which the MEL peak was reduced by 50%, we demonstrated an increase in dopaminergic activity characterized by an increase in DA and metabolite (DOPAC; HVA) content in the striatum [42].

MEL may also directly modulate striatal dopaminergic receptor function. Two weeks of exogenous MEL in drinking water increased the affinity of striatal D2 receptors for MEL [84]. Another line of evidence in support of direct modulation of D2 receptor function by MEL is that iontophoretic treatment with MEL decreased neuronal firing in rat striatal neurons and this effect was reversed by treatment with a D2 antagonist [85]. Moreover, it has been reported that MEL receptors (MT1) and DA D2 receptors colocalize in the striatum and nucleus accumbens [86]. These data support the hypothesis of a MEL/dopaminergic interaction in D2 receptor function in these brain areas and suggest that DA autoreceptors may be involved in the regulation of DA functions by MEL.

7. Conclusion

The relationships between n-3 PUFA and emotional responses and hyperactive symptoms are not well understood. In this review, we highlighted the main findings of studies linking n-3 PUFA deficiency, hyperactivity, emotional response and alterations in dopaminergic transmission. Because MEL is implicated in the regulation of DA pathways and is sensitive to the level of n-3 PUFAs in the brain, we speculate on a possible mechanism by which n-3 PUFA may interfere on DA level. Thus, as illustrated in Fig. 3, we suggest that the drop in MEL is a significant element of the impact of n-3 PUFA deficiency on DA function in the striatum and nucleus accumbens. However, because of the complex nature of neuronal circuitry in this brain region, interactions with other neurotransmitters need to be considered when interpreting these results. The principal neurons in both the striatum and nucleus accumbens are spiny GABA neurons that receive convergent synaptic inputs from glutamate and DA afferences.

A number of studies have also reported inhibitory effects for MEL on glutamatergic activity in the rat striatum [79,85,87,88]. Despite a lack of direct glutamate–DA synapses in the striatum and nucleus accumbens, significant correlations between increases in glutamate and DA were found in both the striatum and nucleus accumbens [89,90]. Because pineal MEL content and release were reduced in n-3 PUFA-deficient rats and hamsters, we postulate that hyperdopaminergia in the striatum is associated with an increase in glutamatergic activity. The hyperactivity and the emotional disturbances that we observed in n-3 PUFA-deficient animals could then be partly explained by a MEL-induced dysregulation of glutamatergic and dopaminergic neurotransmission. This hypothesis could be validated by measuring the levels of glutamate release and content in the striatum of n-3-PUFA-deficient animals. Moreover, it should be remembered that early developmental deficiency of n-3 PUFAs, DHA in particular, may result in a cascade of suboptimal development of neurotransmitter systems, especially in limbic structures, leading to altered emotional and cognitive responses to subsequent environmental challenges.

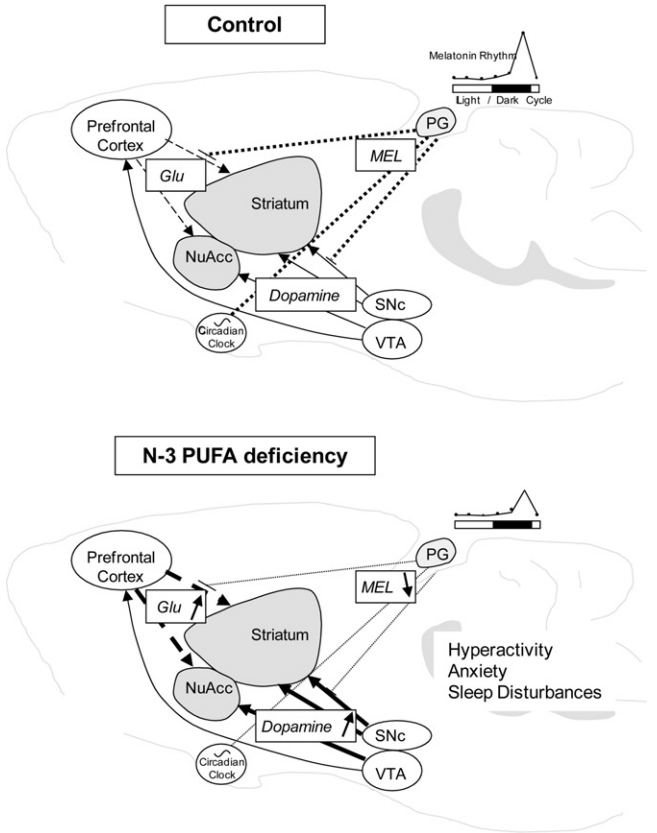

Fig. 3. Schematic diagram showing the suggested mechanisms through which melatonin (MEL) may contribute to hyperactive and emotional exhibition in n-3 polyunsaturated fatty acid (PUFA)-deficient rodents. Upper panel: in the n-6/n-3 PUFA balanced condition, MEL has an inhibitory effect on the dopaminergic and glutamatergic inputs to the striatum and nucleus accumbens (NuAcc) and regulates the endogenous functioning of the circadian clock. Lower panel: in the n-3 PUFA-deficient condition, dampening of the MEL rhythm induces activation of dopaminergic and glutamatergic functions, weakens the circadian clock and thus plays a role in sleep/wake rhythm and in hyperactive and emotional behaviors. Dotted lines represent MEL impact; black arrows represent dopaminergic connections; dashed arrows represent glutamatergic connections. Glu, Glutamate; PG, pineal gland; SNc, substantia nigra compacta; VTA, ventral tegmental area.

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