BBA Clinical 3 (2015) 289–298

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Review

Multifactorial determinants of cognition — Thyroid function is not the only one

Roy Moncayo *, Karina Ortner

Department of Nuclear Medicine, Medical University of Innsbruck, Innsbruck, Austria

ARTICLE INFO

Article history:
Received 31 December 2014
Received in revised form 11 April 2015
Accepted 14 April 2015
Available online 22 April 2015

Keywords:
Cognition
Thyroid function
Magnesium
Prenatal maternal stress
Hippocampus
NMDA receptors

ABSTRACT

Background: Since the 1960s hypothyroidism together with iodine deficiency have been considered to be a principal determinant of cognition development. Following iodine supplementation programs and improved treatment options for hypothyroidism this relation might not be valid in 2015. On the other hand neurosciences have added different inputs also related to cognition.
Scope of review: We will examine the characteristics of the original and current publications on thyroid function and cognition and also add some general determinants of intelligence and cognition. One central issue for us is the relation of stress to cognition knowing that both physical and psychological stress, are frequent elements in subjects with thyroid dysfunction. We have considered a special type of stress called pre-natal stress which can influence cognitive functions. Fear and anxiety can be intermingled requiring mechanisms of fear extinction.
Major conclusions: Recent studies have failed to show an influence of thyroid medication during pregnancy on intellectual development. Neuroscience offers a better explanation of cognition than hypothyroidism and iodine deficiency. Additional factors relevant to cognition are nutrition, infection, prenatal stress, and early life stress. In turn stress is related to low magnesium levels. Magnesium supplementation can correct both latent hypothyroidism and acquired mild cognitive deficits.
General significance: Cognition is a complex process that depends on many determinants and not only on thyroid function. Magnesium deficiency appears to be a basic mechanism for changes in thyroid function as well as of cognition.

Contents

* Corresponding author at: Department of Nuclear Medicine, Medical University of Innsbruck, 6020 Innsbruck, Austria.
E-mail addresses: Roy.Moncayo@i-med.ac.at (R. Moncayo), Karina.Ortner@student.i-med.ac.at (K. Ortner).

http://dx.doi.org/10.1016/j.bbacli.2015.04.002

1. Introductory remarks

Cognition is a term referring to the mental processes involved in gaining knowledge and comprehension. These processes include thinking, knowing, remembering, judging, and problem-solving. These are higher-level functions of the brain and encompass language, imagination, perception, and planning.[1] Evaluation of cognition or intelligence quotient (IQ) is a complex field [1]. Details on how to make such evaluations will not be dealt with here.

Since the 1960s a relationship between hypothyroidism, iodine deficiency and alterations in cognition has been described. These concepts have been maintained for more than 50 years. Due to advances in medical health care the validity of this old postulate might not hold in 2015. This should be kept in mind especially since the condition of iodine supply in the world is improving [2] while at the same time treatment of hypothyroidism with pharmaceutical preparations of thyroxine is being further developed [3]. Apart from iodine deficiency we have recently described a novel player in the regulation of thyroid function and morphology, i.e. magnesium. Low magnesium levels can originate from both physical and psychological stress and these stressors can be found both in hyper—as well as in hypothyroidism. Correction of magnesium deficiency with magnesium citrate can improve both thyroid function as well as slight cognitive deficits seen parallel to acquired thyroid dysfunction [4–6].

Looking outside the field of thyroidology one can find that modern neuroscience research has contributed different insights related to cognition. Unfortunately current studies on cognition and thyroid function do not consider these other inputs [7]. Due to this dichotomist situation we felt that it was imperative to at least enumerate current concepts and factors related to cognition. The individual sections will describe the following: the dogma of the relation to thyroid function, general factors related to cognition such as nutrition and infections, economics, pre-natal stress, stress and telomerase, fear extinction, and the role of the cerebellum and of the hippocampus. Since there is until now no integrative approach to cognition that would unite these elements, the reader is advised to go through each section individually.

2. General factors that can influence cognition and IQ

Searching the medical literature with the terms: “determinants of intelligence” one can find conditions such as body weight at birth [8–10], the duration of pregnancy [11,12], and birth order [13,14] as factors that influence intelligence development. Social conditions have also been described as strong predictors of the IQ of the child [15]. Drug interactions on cognition are also known, e.g. the classical antihistamine, D-chlorpheniramine [16]. Choline imprinting can also modify cognition [17]. Thus strategies or suggestions that consider choline supplementation have appeared [18]. Brain development and vitamin B have also been presented in the literature [19].

2.1. Nutrition

In 1995 Grantham-McGregor scrutinized the effects of severe malnutrition on mental development [20]: after early life malnutrition IQ levels can be poor. The author concluded that the outcome depends on the quality of the environment (see also the discussion on economics in Section 4). In an experimental environment Strupp and Levitsky described a connection between early malnutrition and changes in emotionality and even anxiety [21]. Malnourished children can show alterations in working memory, visual construction, learning and memory [22]. Byrd-Bredbenner et al. looked at the link between social cognitive competence and the mothers' dietary intake and BMI. They found out that women in the lowest tertile on the Likert scale consumed significantly less fiber, vitamin C, magnesium, potassium and fruit and vegetables than the upper tertiles [23]. Marques and coauthors examined the combined situation of early childhood nutrition as well as maternal prenatal stress in relation to immune system development and neurodevelopmental changes. They found out that adequate nutrition is necessary to establish an immune system as well as an adequate immune response; this is so important because the immune system may modulate the risk for later neurodevelopmental diseases [24].

2.2. Adolescent mothers

Adolescent mothers and the effect of their early responsibility to another life are a controversial subject. Camp described the negative influence of adolescent mothers to the development of the children: more children than expected had high scores on scales for hyperactivity and academic disability [25]. Sommer et al. suggested that only 28% of the children born by adolescent mothers scored within normal ranges on personal adjustment and intellectual–linguistic development, social–emotional functioning, and adaptive behavior at age 3 years [26].

2.3. Early life stress in the form of infection, trauma and inflammation

The literature suggests that both prenatal infections and traumatizing experiences during the time prior to puberty might cause harm to the children, e.g. they are suspected to increase the risk to be diseased with neuropsychiatric disorders later in life. Giovanoli et al. examined these happenings in a mouse model and found out that they induce “synergistic pathological effects on adult behavioral functions and neurochemistry” [27]. Furthermore, they suggested that “the prenatal insult markedly increases the vulnerability of the pubescent offspring to brain immune changes in response to stress”. The observations by Wadhwa and colleagues let one assume that infections during pregnancy, especially maternal urogenital tract infections, are a risk factor for preterm birth, which is one of the most important obstetrical problems in the United States [28]. Besides, Tough et al. found evidence that maternal mental health might influence the development of the children and can cause problems for the toddlers at age 3 [29].

3. Studies on the relation between thyroid function and IQ development

In this section we will refer to key publications dealing with the development of children in relation to maternal thyroid dysfunction. We have excluded studies describing the situation of congenital hypothyroidism.

Early reports on the association between disturbed thyroid function and child development were done at a time when only simple laboratory evaluations were available. The method used was that of the determination of butanol extractable iodine (BEI). A description of the basic chemical process for iodine determination was made by Bauman in 1895 [30]. Man et al. presented the method for the determination of BEI in the 1950s [31].

[1] http://psychology.about.com/od/cindex/g/def_cognition.htm.

3.1. Thyroid function, obstetrical pathology, and cognitive development — early studies

In 1960 Greenman et al. reported the course of child development in relation to different states of thyroid function [32]. They included 22 women divided into 4 groups with known or suspected thyroid disorders during 23 pregnancies. In seven cases hypothyroidism was due to previous thyroidectomy. A second group included 7 women who had low BEI values and who were considered to have probably hypothyroidism. The third group included 6 women with similar characteristics as those found in group 2, however BEI values were higher. Group 4 included 3 patients with hyperthyroidism. The authors followed 23 pregnancies. One year after termination of pregnancy 18 children were alive and 5 children were described as being abnormal. The most marked alterations were observed in study group 2, i.e. low BEI levels. This group would now be classified as untreated hypothyroidism. There were 3 children with mental retardation, 1 stillbirth and 1 abortion; only one child was classified as normal.

3.2. Studies from Elisabeth Man and work in Western New Guinea

Elisabeth Man and coworkers described in 1968 the features of premature children born in the 8th month of pregnancy [33]. The field nurse involved in this study reported that in many of the homes of these women with gestational hypothyroxinemia the socioeconomic conditions were not optimal. Data evaluation showed lower IQ values to be associated with low BEI levels in untreated hypothyroid women [34]. Low IQ levels, however, were also seen in children from mothers with euthyroid function. In this publication Man mentions other factors that should be considered in relation to IQ levels. These are: socioeconomic conditions, poor diet and malnutrition of the mother during gestation as well as of the infant in early life.

In the Addendum of the 1969 publication [33] the authors mention the work of Adams referring to endemic goiter in Western New Guinea [35]. Adams et al. reported a situation of gross iodine deficiency in the Mulia Valley of Western New Guinea. TSH was determined using the McKenzie bioassay. Comparing subjects with mental deficiency, motor abnormalities, deafness or deaf-mutism to non-defective people they found however no differences in TSH levels.

3.3. New Guinea and the man-made iodine deficiency condition

The mention of New Guinea as the setting for studying conditions of thyroid disease deserves an extra comment. The native population was basically enclosed in the highlands of Western New Guinea (WNG) [36]. Their main source of salt came from natural salines located in a volcanic area [37]. Volcanic areas are known to contain also selenium [38]. The introduction of capitalistic economy methods brought also the use of refined salt. The socio-economic aspects of this process of monetization produced a collapse in a pre-capitalist tribal economy which had been able to maintain a self-sufficient status [39]. By this external measure the population lost their natural nutritional sources and lost also sources of selenium and iodine. The effect of this measure can be clearly seen in Fig. 2 on page 795 of a later paper by Pharoah [40] where the rise of goiter incidence follows the introduction of refined salt. In addition to this the daily protein intake was described as being much lower than the European standards of that time which means that malnutrition was also present [41]. Selenium intake studied in 1992 was found to be extremely low [42]. The combined factor of protein-caloric malnutrition together with chronic iodine deficiency has indeed been described by Fierro-Benítez et al. in Ecuador in connection with cognitive defects in children [43].

An account presented by Pharoah mentioned the use of a tool for intellectual performance, i.e. the Pacific Design Construction Test [44]. With this tool the authors claimed to have found that the population had difficulties in dealing with a picture-based test. It has to be outlined that the testing relied largely on non-verbal instructions, thus no direct language contact was involved. By this the test and the investigators introduced a foreign tool unrelated to the population. Looking back at this publication one finds that a quite unusual test was also utilized: to insert plastic pegs in a pegboard. Although the authors did not consider bias due to these tests they concluded that the population examined had deficits in motor and cognitive performance. Modern statistical methods would cast doubt as to the appropriate size of the sample which was extremely limited to 20 subjects. Extrapolating this approach to modern days one could elaborate that Rubik's cube could replace intelligence tests and introduce new concepts for cognition [45].

A graphical summary of the key publications which appeared between 1962 and 1971 is shown in Fig. 1.

3.4. What is valid in 2015?

The basic studies cited here were conducted several decades ago. At that time iodine deficiency was a central issue. In addition to this some subjects presented some type pathology, e.g. premature infants, and mothers had untreated hypothyroidism. Summing up these previous investigations Bougma et al. 2013 presented a meta-analysis of data on iodine supplementation and mental retardation [46]. The authors described indeed the beneficial effect of iodine supplementation. By reading this publication one could believe that iodine deficiency is still prevalent now at the same rates as it was in the 1960s and will affect newborns also. Using a similar approach Zhou et al. have analyzed in 2013 the data on iodine supplementation and cognitive function of children [47]. They commented that there is a lack of quality evidence on the benefit of prenatal or peri-conceptional iodine supplementation on cognitive function of children. Zhou et al. pointed out the results reported by Lazarus where the authors had failed to find a positive effect on cognitive function at age 3 years by carrying out antenatal screening and maternal treatment of hypothyroidism [48]. This study is currently being pursued aiming at evaluation of cognition at a later age [7].

One forgotten aspect in such meta-analysis is to follow-up the initial descriptions of pathology. Following iodine supplementation programs this health problem has been eliminated or reduced in some countries but not in all. This can be demonstrated by the situation in Ecuador. One of the authors of this review (RM) started his scientific work on this topic back in 1976 under the guidance of Prof. Rodrigo Fierro-Benítez in Quito, Ecuador and the support of Prof. John B. Stanbury of the Massachusetts Institute of Technology [49]. Following iodine supplementation programs iodine deficiency was corrected by 1994 [50]. A later press report in 2013 confirmed the success of the iodine supplementation program in Ecuador.[2] A similar situation can be observed in Austria following iodine supplementation. The initial picture was that of iodine deficiency goiter [51]. We have recently dealt with this question indirectly while evaluating thyroid function parameters in normal pregnancies. Since iodine supply is sufficient it is now not uncommon to observe hyperthyroidism developing in pregnant women who receive extra iodine supplements [52]. Therefore the indiscriminate recommendation to increase iodine supply in normal pregnancies could do more harm if the population is iodine sufficient.

If the studied population bears similarities to those described by Man [33] (Fig. 1), i.e. premature babies with hypothyroxinemia, the negative results on IQ can be similar [53]. The question of hypothyroxinemia leads us to the way on how to detect such cases. After the days of BEI determinations the way to detect altered thyroid function in pregnant women is through validated laboratory reference values. We have recently presented such reference values for an iodine sufficient population [52]. Our validated biochemical approach contradicts the use of artificially defined low upper levels of TSH in pregnancy [54]. The use

[2] http://www.andes.info.ec/es/sociedad/bocio-cretinismo-endemico-erradicaron-ecuador-gracias-controles-niveles-yodo-sal.html.

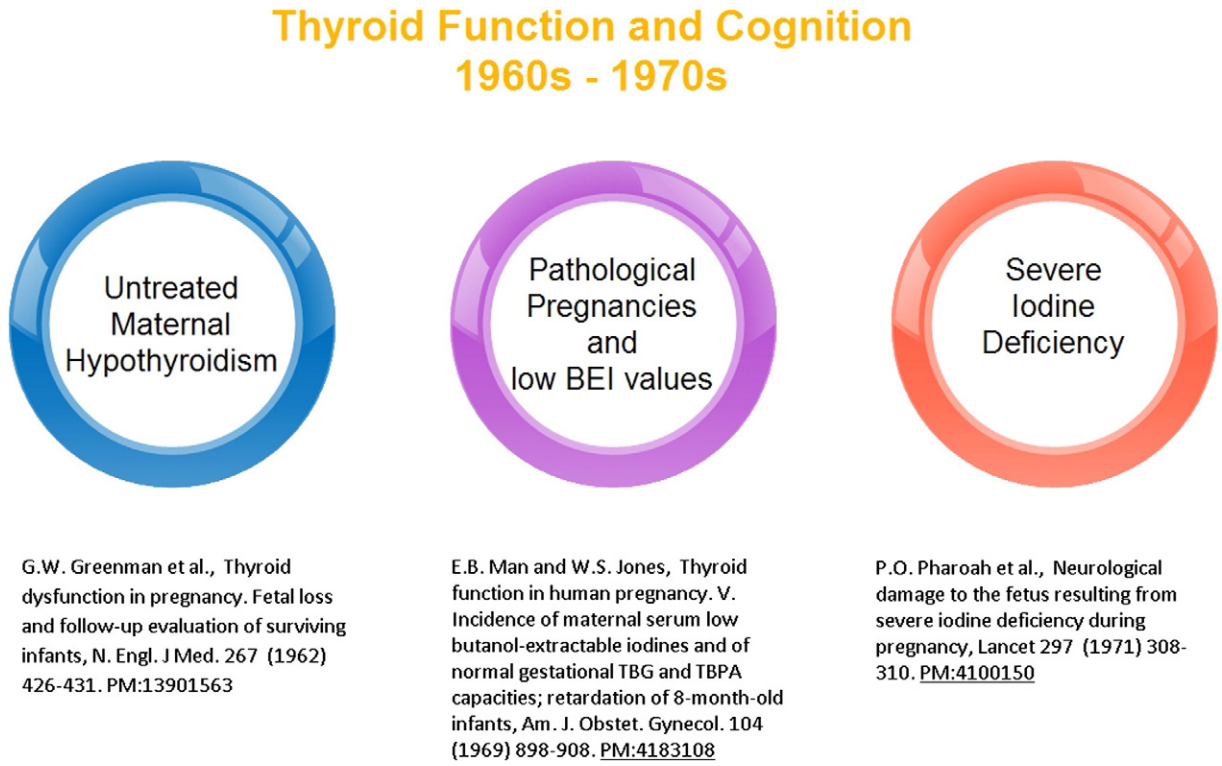

Fig. 1. Central issues relating thyroid function to cognition. It has to be noted that each publication described additional pathology during pregnancy (untreated maternal hypothyroidism, pathological pregnancies and low BEI levels, and severe iodine deficiency).

of lower upper reference values of TSH would unnecessarily turn normal euthyroid subjects into cases of hypothyroidism. We have previously analyzed the negative consequences of such approach for adults [55]. Recently we have also expressed our doubts on applying such artificial TSH reference values in the field of fertility. Such an action would only contribute to added emotional stress [56]. We have to mention here that women with recurrent pregnancy loss are affected by depression and emotional stress [57]. In the following sections we will discuss the role of such stress situations which can be termed prenatal maternal stress.

To close this section we will briefly describe the results of an interventional study entitled: "Antenatal thyroid screening and childhood cognitive function" [48]. The main result is that the study failed to show any effect of thyroxine administration on cognition. This lack of effect can be explained by the fact that the majority of women had normal TSH values (Table 1 in [48]).

To close this section it can be stated that what constitutes a risk profile for possible IQ alterations of the progeny is obstetrical pathology, overt hypothyroxinemia or untreated hypothyroidism, and prematurity. Normal TSH values, i.e. 0.–3 to 3.5 miU/l, do not predict a positive effect of thyroxine administration on cognition.

4. Can economics offer an explanation for health and models of prenatal stress?

In 1972 Grossman presented a thesis entitled: "On the concept of Health Capital and the Demand for Health" [58]. Although the concept has originated much resonance (4390 citations, Google Scholar, accessed April 11th, 2015)[3] from our point of view it is not applicable in the medical area. For example it does not consider that health stock could already be altered prior to birth nor does it consider quality in health care. The text is oriented to point out quantity. We believe that a purely capitalistic approach where the author uses the term "human capital" is not the best one to deal with health objectives. Another misconception is that of health being a consumption commodity which results in disutility caused by sick days. While the author stresses that net investment in the stock of health equals gross investment minus depreciation, it leaves no room for measures that improve health and thus prevent depreciation. In equation 9 in Grossman's thesis full wealth is characterized as the sum of initial assets plus the present value of the earnings. This simplistic view ignores economic situations where professional life begins with a negative economic balance, e.g. student debts. This type of situations has been described to be related to poorer physical health [59]. In such a situation the person starts into productive life having a negative financial balance. Some of the problematic situations can be handled or not by the parents according to their capabilities [60]. In addition the level of worry, either high or low, in relation to the student's debt will have an influence on mental health [61].

The relation between economics, cognition and early life influences has been considered as a complementary whole in recent studies. While we do not agree with Grossman's limited model as being directly applicable to health, the economic descriptors he used can be taken as a simile to human postnatal development. In 2006 James J. Heckmann combined the concepts of health and economics and added the description that relates them to early life situations [62]. Skogen and Overland have recently commented on this hypothesis of fetal origins of adult disease (FOAD) from an epidemiological view [63]. In 2007 Heckmann described the interactions between health economics and the human capital approach as well as the economics related to cognitive and non-cognitive skill formation mentioning a panel of 9 (relevant?) items [62]. In his article "The developmental origins of health" [64] he added a framework used to analyze the expression and evolution of capabilities. The reader can extract that one central element is cognition however the author did not deliver a suggestion as how to remediate cognitive capabilities. The final conclusion of the article states: "We need to trace the effects of early-life outcomes on intermediate-life

[3] http://scholar.google.com/citations?user=HlgG1z4AAAAJ&hl=de.

investments and environments in order to understand when and for what intervention can be effective".

4.1. Intellectual fusion in cognition research

In 2006 Knudsen [65] defined their research focus in this field as follows: "This paper focuses on the striking convergence of four core concepts that have emerged from decades of mutually independent research in economics, neuroscience, and developmental psychology. First, the architecture of the brain and the process of skill formation are both influenced by an inextricable interaction between genetics and individual experience. Second, both the mastery of skills that are essential for economic success and the development of their underlying neural pathways follow hierarchical rules in a bottom-up sequence such that later attainments build on foundations that are laid down earlier. Third, cognitive, linguistic, social, and emotional competencies are interdependent, all are shaped powerfully by the experiences of the developing child, and all contribute to success in the workplace. Fourth, although adaptation continues throughout life, human abilities are formed in a predictable sequence of sensitive periods, during which the development of specific neural circuits and the behaviors they mediate are most plastic and, therefore, optimally receptive to environmental influences" [65].

This short account on the role of economics has made an interesting development coming to intellectual fusion between the fields of Neurobiology, Economics, Psychiatry and Social Policy and Management. The concept of early life situations will be taken up in the following sections from a different point of view.

5. The role of the cerebellum in cognition

Besides the classical functions of the cerebellum in control motor activity, some evidence has accumulated indicating a role of this organ in cognition, thus defining a nascent field of work. Noroozian has recently presented a summary of some the developments [66]. We will enumerate some important findings in this new filed in the following lines. In the work done by Leiner et al. [67–69] it was found that the lateral cerebellum is involved in some cognitive and language functions. In 1997 Bloedel and Bracha discussed the dual function of cognition and cerebellar motor capabilities leading to motor coordination and adaptations in behavior [70]. Stoodley has described cognitive networks of the cerebellum which appear to be associated with prefrontal and parietal cortices [71]. Recently Koziol and Lutz proposed an interesting bottom up model of executive function and cognition based on the motor development in children [72]. The authors proposed that: "cognition and EF evolved from the development of the motors system to control it, and in this way, there is no critical difference or duality between motor and cognitive functions". This area can be expanded to include also elements called vestibular cognition [73]. Further aspects related to cerebellar function include spatial cognition in functions such as neural coding, learning, memory and cognition [74] as well as the interrelationship between cerebellum and language [75]. Bernard and Seidler discussed age-related changes in volume of the cerebellum [76]. Bernard et al. have also looked at changes of cerebellar volume in relation to age and cognitive function [77]. In a contribution by Ito which deals with intuition and thought the reader can find an interesting depiction of some of the important cerebellar areas involved in mental activities such as attention task, a future-vision task and a verbal working-memory task (Fig. 5 in [78]).

While going through these new notions on the role of the cerebellum the reader can sense that some of the characteristics mentioned coincide with parameters utilized in intelligence tests. Again, since this is a nascent field or research more can be expected to come in the future.

6. Pre-natal stress

The field of neuro-behavioral development has recognized several factors that appear to have an influence on human development beginning before the birth of a person, i.e. a possible fetal origin of disease. Epidemiologists refer to the so-called Barker theory [79]. Barker described in 1986 a correlation between conditions that were present at about the time of birth as well as at early infancy and the morbidity and mortality of chronic diseases [80]. In 2005 Van den Bergh and colleagues summarized some of the early publications on this field [81]. Not only the developing fetus can be the target of external influences, stress acting on the mother can also affect negatively cognition and be associated with fearfulness in children. This is referred to as "fetal programming" [82]. It has been proposed that fetal origin of adult disease can be the result of nutritional stimuli or of corticosteroids [83]. In 2008 Beydoun reviewed the current literature dealing with the effect of prenatal maternal stress [84].

Additional changes that can be expected to occur after maternal stress are attention deficit hyperactivity disorder, conduct disorder, aggression or anxiety [85]. This situation for example can be related to lower neonatal weight and to low birth weight [86,87]. Besides, a group of researchers from the United States suggest that poor mental health, as well as problems in psychosocial functioning and impaired physical health is an outcome of traumatic exposure. The authors propose to treat the consequences of a PTSD to reduce the influence of this burden on individuals [88]. These effects should not be disregarded since it appears that roughly every woman experiences some kind of prenatal maternal stress (PNMS) during her pregnancy. In addition to this PNMS represents a risk for preterm delivery — the most important problem in maternal–child health in the United States. Wadhwa et al. even developed a model according to which chronic maternal stress is a significant and independent risk factor for preterm birth. They present two possible pathways through which PNMS may act: "(a) a neuroendocrine pathway, wherein maternal stress may ultimately result in premature and/or greater degree of activation of the maternal–placental–fetal endocrine systems that promote parturition; and (b) an immune/inflammatory pathway, wherein maternal stress may modulate characteristics of systemic and local (placental–decidual) immunity to increase susceptibility to intrauterine and fetal infectious–inflammatory processes and thereby promote parturition through pro-inflammatory mechanisms" [28].

Möhler and colleagues demonstrated that infant affective reactivity to novelty was influenced by PNMS, however, postnatal maternal stress was not associated with the toddler reactivity [89]. Another study shows that prenatal maternal stress has a negative influence on both the toddlers' cognition and fearfulness and suggests that the intrauterine development influences the neurodevelopmental and psychiatric outcome. The authors describe that "prenatal stress accounted for 17% of the variance in cognitive ability and 10% of the variance in observed fearfulness" [82]. In another publication the same group of investigators provided preliminary evidence in humans that early caregiving environment might reduce the effects of PNMS on children [90]. Besides, further clinical evidence showed that personal resources and sociocultural context in pregnancy might partly compensate the damage arising from prenatal maternal stress during pregnancy [91].

Laplante and coworkers published in 2004 a study in which they shed light on the effects of prenatal maternal stress on the general intellectual and language functioning in human toddlers [92]. They examined 58 toddlers whose mothers were pregnant during an ice storm in Quebec, Canada, in January 1998 at the age of 2 years. By measuring the infants' Bayley Mental Development Index (MDI) scores and asking the parents for the toddlers' language abilities the researchers found out that "the more severe the level of prenatal stress exposure, the poorer the toddlers' abilities". Laplante et al. postulate that the infants in early pregnancy are most vulnerable to PNMS [92]. This leads us to the question: at which particular time is prenatal maternal stress most

detrimental? Huizink and coworkers have looked at the most vulnerable time in pregnancy for PNMS on the toddlers' development. They examined 170 nulliparous women by collecting salivary cortisol levels in every trimester and asking the women to write down their daily hassles and pregnancy-specific anxiety in a self-report form. When the infants (only those who were born at term) were at age 3 and 8 months their mental and motor development was assessed. The researchers wrote: "High levels of pregnancy-specific anxiety in mid-pregnancy predicted lower mental and motor developmental scores at 8 months ($p < 0.05$). High amounts of daily hassles in early pregnancy were associated with lower mental developmental scores at 8 months ($p < 0.05$) [93]. Early morning values of cortisol in late pregnancy were negatively related to both mental and motor development at 3 months ($p < 0.05$ and $p < 0.005$, respectively) and motor development at 8 months ($p < 0.01$)" [94]. Three years later, a similar group of researchers published a study in which they found out that prenatal maternal stress is especially harmful for the infant's attention/concentration index in the first part of pregnancy [95]. A group of researchers from the United States investigated the influence of pregnancy-specific anxiety, state anxiety and depression on the toddlers' neurodevelopmental outcomes. They interviewed 89 pregnant women at 15, 19, 25, 31 and 37 weeks of gestation to outline their current situation concerning the variables above. At age 6 to 9 years the executive function of the offspring was assessed. "High levels of mean maternal pregnancy-specific anxiety over the course of gestation were associated with lower inhibitory control in girls only and lower visuospatial working memory performance in boys and girls. Higher-state anxiety and depression also were associated with lower visuospatial working memory performance. However, neither state anxiety nor depression explained any additional variance after accounting for pregnancy-specific anxiety. The findings contribute to the literature supporting an association between pregnancy-specific anxiety and cognitive development and extend our knowledge about the persistence of this effect until middle childhood" [93]. Anxiety has also been found to be related to non-optimal neuro-motor development [96].

Glynn and coworkers examined the effects of negative life stress happening during pregnancy and the emotional response to it. They included 292 women into their study and suggested that specific life events occurring early in pregnancy are perceived as more stressful to the mothers-to-be [97]. Recently the same group of investigators proposed that maternal psychosocial stress can affect the stress regulation response of the infant [98].

6.1. Anxiety, cognition, telomerase activity and the role of psychological stress

A further central issue involved in this complex is psychological stress which needs to be identified and treated. Recent data has pointed out the effect of adversities in early life which influence physiological regulation in later life [99]. While the original theories of Selye on the general adaptation syndrome as a response to a general alarm reaction [100] initiated research on the hormones of the HPA, recent experimental research has clearly demonstrated that the endocrine response pattern associated with stress reactions can be triggered by a condition of magnesium deficiency. This leads to a situation of anxiety and to activation of the HPA axis [101]. Altogether we believe that it is sensible to propose that as a consequence of the negative effects of the physical and psychological stressors magnesium levels decrease creating a situation which increases the general susceptibility to stress [102]. Low levels of magnesium will add another negative dimension to the organism, i.e. downregulation of telomerase [103]. On the other hand and contrasting with chronic stressors, acute stress has been considered to be beneficial as it stimulates neurogenesis in the hippocampus under experimental conditions [104].

Cognitive impairments and fear generalization have some common elements that can be linked to magnesium, selenium and coenzyme Q10 as well as to the hippocampus. In order to describe these links we cite here some clinical and experimental data in a chronological order which corresponds roughly to life development.

The main terms describing this setting are maternal prenatal stress and early life stress. In a similar way research on epigenetics goes even to consider a broader time window. Citing Lo and Zhou [105]: "There are three categorical stages of life history when epigenetics are registered — ancestral (including parents), prenatal, and postnatal stages. Among these stages, prenatal epigenetic registration is the most eminent and profound influence on the formation or fine-tuning of the nervous system during development." We consider that the starting point in clinical work should consider prenatal maternal stress which can be seen as a contributing factor to stress conduct later in life [106–108]. Besides this, events happening in intrauterine life can also affect telomere length in the newborn [109] as well as in young adulthood [110]. These events together with the interaction of low magnesium levels with telomerase mentioned above let us propose a tighter connection between magnesium deficiency, stress, and future development.

We have described prenatal maternal stress in a previous section. These effects show changes in the function of the hippocampus [111]. Early life stress has been found to shape areas of the brain related to emotion processing located on the hippocampus and amygdala [112] and early life stress can be related to hippocampal cell loss [113] as well as to inhibition of neurogenesis [114]. Experimental studies on prenatal stress have demonstrated an alteration in the neurogenesis of the hippocampus thus consequently affecting the learning capability [115]. The timing of these situations, i.e. pregnancy [116], is directly related to the concept of pre-natal stress. Ante-natal stress has also been considered as a possible origin of later psychopathology [85,117]. Both intellectual functioning and cognitive ability or development can be affected in children [82,92,118–120]. Contrary to pre-natal stress, maternal care promotes hippocampal synaptogenesis and in the end cognitive development [121]. This function is related to the brain-derived neurotrophic factor (BDNF). Selenium exerts neuro-protective action on the hippocampus in relation to BDNF [122]. One important mechanism that is found in cases of maltreatment is DNA methylation of BDNF [123]. Szyf considers DNA methylation a mechanism by which experiences in early life can be embedded [124,125]. Experimental magnesium deficiency during pregnancy has been found to be related to hyper-methylation [126]. An additional mechanism related to intrauterine stress is the appearance of shorter telomeres in young adults [110]. The Alturas have recently demonstrated that short-term magnesium deficiency can down regulate telomerase [103]. In addition to this, Bachnas et al. have shown that antenatal supplementation with magnesium sulfate in humans can improve the levels of BDNF [127]. In the setting of experimental menopause, Sandhir et al. have found that coenzyme Q10 can ameliorate cognitive functions [128]. Low selenium levels in elderly people can be associated with cognitive decline [129]. Exciting experimental data have been recently presented by Abumaria et al. on the beneficial effect of magnesium supplementation using a new compound magnesium L-threonate. It is effective in preventing fear over generalization [130] and it can also enhance the retention of the extinction of fear memory [131]. Wang et al. have observed that magnesium L-threonate can prevent and restore memory deficits related to neuropathic pain involving TNF-alpha [132]. Cognitive functions such as learning can also be positively modulated by magnesium administration. This last action is related (again) to changes in the hippocampus [133]. These experimental findings are of interest to our research because they correlate with the effects of thyroid function on the hippocampus [134–137] as well as to psychological stress due to trauma [102,138–140].

6.2. Fear extinction

Some situations mentioned in the preceding sections have to be seen from overcoming adversities. In order to achieve this, a mechanism of

fear extinction will be needed for reducing conditioned fear responses [141]. This has a place in this review since learning to overcome adversities involves cognitive processes [142]. When fear extinction cannot be mastered a relapse of fear can occur [143]. Anatomical correlates in the brain include the medial pre-frontal cortex and the hippocampus [144–146]. Orsini and Maren have reviewed data on the field of fear and extinction memory formation at a neural and cellular level [147].

Estrogen levels have been described as potential regulators of these processes both in humans as well as under experimental conditions [148–152]. While interventions with hormones could have a potential use [153], a rather simple measure to influence fear conditioning appears to be the administration of magnesium aiming at increasing its levels in the brain [131]. On molecular grounds, magnesium administration will influence the expression of the NR2B component of the NMDA receptor in the hippocampus [154].

7. Neurocognitive research, stress and the NMDA receptor

Synaptic plasticity in the processes of learning and memory is related to the N-methyl-D-aspartate (NMDA) receptors [155]. In the rat 3 species of coding DNA for the NMDA receptor have been identified. The subunits coded are NMDAR2A, NMDAR2B, and NMDAR2C which are also called NR2A, NR2B, and NR2C [156]. These subunits will form heterodimers which have different properties. In the developing brain of neonates functional interactions between NMDAR and magnesium are lesser than to the ones found from glutamate and glycine [157]. On the other hand post-mortem investigations of the brain in cases of cognition in schizophrenia have shown a significant correlation between NR-1 mRNA loss and cognitive deterioration [158].

Besides the elements mentioned here, recent research on cognition has expanded its scope looking into stress situations. This feature links this section with the previous ones. Following the opinion of Pessoa [159] it appears wise to consider cognition and affection together. Working with adults Navalta et al. have demonstrated that repeated sexual trauma in childhood can affect cognition in apparently healthy adult women [160]. Such stressful situations could affect neurogenesis of the hippocampus [161]. As mentioned above one mechanism that is involved in lessening the influence of previous stress situations is consolidation of fear extinction which is a process that requires activation of the NMDA receptors [162]. The C-terminal intracellular domain of the GluN2B subunit has been further characterized to be involved in fear memories and fear extinction [163]. The NMDA receptor is also related to memory and chronic pain. Zhuo has pointed out the relationship of the NR2B subunit in this context [164].

Besides fear extinction, the process of aging has been shown to be associated to a deficit in NR2B which in turn relates to learning and memory [165]. Wang et al. have recently discussed the option of targeting the NR2B subunit of the NMDA receptor for improving memory functions. The use of magnesium L-threonate has been found to be useful in upregulating NR2B expression [166].

Synaptic plasticity involves not only NMDA receptors and BDNF but also reelin. This action appears to be mediated via the ApoE2 receptor [167,168]. The ApoE2 receptor functions also as a receptor for selenoprotein P. Alterations in this system will lead to neurodegenerative changes [169]. In addition to this, thyroid hormones regulate reelin expression and thus neuronal migration [170].

Zinc deficiency will have a negative effect on the development NMDA receptor subunits [171]. Zinc deficiency can also affect neurogenesis [172–174] and also affect cognition [175]. Zinc supplementation increases BDNF levels and can delay influence the appearance of memory deficits and also improve mitochondrial function, i.e. respiratory complexes I, II, and IV [176].

8. Magnesium: a new therapeutic option in stress and in thyroid function and neuro cognitive research

In recent studies we have been able to demonstrate a functional relationship between magnesium levels and thyroid function, i.e. TSH levels, as well as vascularization [4,5]. Two special conditions were found to be associated with this situation: physical stressors in the form of musculoskeletal changes and psychological stressors. The common denominator associated with them is that of low levels of magnesium. Clinically some of the adult patients report having fatigue as a central complaint. Cognitive difficulties such as lack of concentration, difficulties in learning, and forgetting things were also present. Treating these patients in a holistic way to include the physical and psychological problems led to improvement of a great majority of symptoms. In cases of hyperthyroidism as well as of hypothyroidism thyroid morphology returned to normal after long-time supplementation with magnesium citrate, i.e. 3–5 years. Some patients required also coenzyme Q10 when characteristic changes in the vessels were found, i.e. thickened vessels [5]. On the other hand patients presenting acute situations of anxiety and fear tended to present a drop in the concentration of magnesium without changes in thyroid function.

Parallel to our studies and developments the group from Guosong Liu was working on the relation between magnesium and cognition. In a series of publications they were able to show the positive effects of a novel magnesium salt, i.e. magnesium L-threonate. The effects included enhancement of memory and learning. It also modulated fear extinction and fear conditioning and prevented fear overgeneralization [130,131,133,177].

Based on our clinical observations we propose that magnesium levels in blood appear to reflect rapid physiological changes following stress. Besides the theoretical considerations presented here it appears necessary to design a simple therapeutical approach for the individual. Using the proposal from Griagnic-Philippe et al. one could look at: “Measures of subjective psychological stress and objective physiological stress responses offer different information and their simultaneous use would allow us to obtain a more global picture” [178]. Institution of magnesium supplementation with magnesium citrate could have the potential to neutralize the effect of stressors found prior to pregnancy or during pregnancy, i.e. ancestral or prenatal stress, and thus improve outcome of the offspring including consequently cognition. This concept follows the recent findings of Sartori et al. who clearly demonstrated that the activation of the stress reactions can be reduced to magnesium deficiency [101]. Lack of magnesium will limit achievement in the sense of resilience [4].

Closing our discussion of cognition we would like to include a quote of a publication by Bay [179] who looked at the interactions between fertility treatments and IQ: “This study confirms that adjusting for parental intelligence should be the norm when examining child IQ as an outcome. Another elegant feature is inclusion of a range of child cognitive outcomes: IQ, attention, and executive function”.

9. Limitations of the review

Our academic review had a starting point in the field of thyroid diseases. The inclusion of a larger scope of information outside of our central area of work was done with the best of our cognitive abilities.

Contributions

Both authors contributed equally to literature research. Both authors wrote the draft. RM wrote the final version and produced the graphical abstract.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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