ORIGINAL ARTICLE

Formative Processes of CNS Maturation – The Genesis of Neuropsychiatric Disorders and the Strategy of Optimal Development

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Abstract

Understanding the development of organism and especially the nervous system maturation has been continuously enriched by many new discoveries whose significance is to be recognized in the future. Authors discuss the role of some epigenetic factors (e.g. nutrition, quality of maternal care) and the mechanism of their action in the nervous circuits maturation, development of cognitive functions or in the neuropathology of neuropsychiatric disorders.

Introduction

Identification of factors (beside the genetic ones) that control the development and differentiation of the Central Nervous System (CNS), its individual parts, and neuronal circuits represents a pursuit race with new and new data. Starting with the deep past it is possible to quote Prochaska (1784) who characterized the nervous system as a complex system with multiple functions.

To simplify classification of the immense set of factors which control or modulate the maturation of CNS, three major domains are suggested: The first domain includes factors that act by means of stimulation of the sensory input of the organism (intensity, duration, character of the stimuli). Effects of impoverished or enriched environment were many times studied with comparatively coherent results: The enriched environment can accelerate maturation and bring the activity of neuronal circuits to the optimal functional level.

The second domain includes factors that determine the nutritional status. The vast array of relevant data convincingly confirms that the nutritional deprivation can radically impair the CNS development, namely during periods of higher energetic or substrate demands (critical periods). Individual nutritional components (amino acids, vitamins, trace elements) were examined with definite conclusion: Developing organism (and the brain) requires a long list of nutrients and any deprivation brings negative effects. Consequences are either generalized - delay in the development, structural or functional impairment (immunity, motor performance, adaptability) or specific for deprivation from individual components of nutrition.

Negative effects which may bring factors of the first and second domain can bring extensive social problems (psychology, sociology, economy, education, judicial system) as well as the involvement of the health care. More medically oriented problems can

bring factors of the third domain. They can be labelled as factors with pathogenetic effects. Those epigenetic factors are related to the dysgenic effects of industry, namely the pharmaceutical one, to the new methods of food conservation, and to the abuse of drugs and related substances.

The most fascinating in the developmental studies is that the enormous variety of different known and yet unknown epigenetic factors can act by means of a few mechanisms. One of them is the direct effect on the genetic code. More frequent are however much more discrete effects in the gene transcription-translation process, including the small cytoplasmic RNA molecules.

The aim of the presented article is to draw the attention on those mechanisms which participate in the control of CNS maturation but which are not yet fully discussed and respected and still play an identifiable role.

Maternal behaviour, maturation and pseudoheredity

There is no doubt, that many complex effects and factors in early stages of development may and in fact influence the development of the organism including its consequently evolving disposition or sensitivity to various diseases. Such findings analysed in particular cases, in experiments or in summary reviews are continually growing. Thus showing floating limits in contrast to interpretations offered by genetics in 1970´s and 1980´s: its, that time, non-complicated determinism had been more acceptable then very "diversity of possibilities related to aspects of certain doubts" (represented by studies on environmental effects on the final product).

Brain with its unrestrained embryonic and early postnatal period is an organ which is, besides genetic factors, exposed to many complex and complicated effects. Such effects have not only different character but also different weight of evidence. More over, there is a "time schedule" of the general development with cascade of bilateral conditional ties. It is therefore not unconcerned where, with what intensity, with what duration, these effects will act. Some specific effects and conditions are assumed and provided by genetic program itself (e.g. type of nutrition, thermal optimum, physiological stimulation fields etc.). Genetic program can not be implemented without such conditions of organism (and brain particularly) maturation. These conditions are therefore having an essential character.

Changes – although having character of subtle deviations – of intrinsic development may arise just as a consequence of such deviations of mentioned key conditions in early stages of ontogenesis. These changes can then propagate into future generations.

These problems were opened on a theoretical level for more than 50 years ago and were relatively well and accurately formulated, resulting in findings, interpretations and analysis which attained clinical part much later. The disorder of offspring care (more accurately disorder of maternal behaviour) had been in past the objective of series of experimental studies (Dobbing 1964, 1968; Mourek 1959, 1960; summarily Mourek *et al* 1974; Novakova *et al* 1962; Novakova 1966; Myslivecek *et al* 1966; Widdowson & McChance 1963, Winic & Noble 1966; Novakova *et al* 1972).

The deviation of maternal behaviour, its insufficiency, represents very serious interference with the program of newborn's development including the development of CNS (central nervous system) and neurohumoral regulations. This vulnerable period of brain against e.g. any kind of nutritional deprivation (all forms of malnutrition, underfeeding, early weaning etc.) is evolutionary in such a concern that it indicates – in various extension – long term and usually permanent consequences.

Typical examples are experiments with alteration of laboratory-rat female development. Nutritional deprivation (even short termed!) causes not only deceleration of development but demonstrably comes to maturation distortion of such integrated structures and functions of CNS as e.g. learning, memory, memory track retention, exploration, habituation, spatial orientation. Also violation of "maternal behaviour" complex occurs (Frankova 1966, 1971). Carrying of offspring to the nest, thermal stability of the nest, process of breastfeeding as well as stimulation of offspring's miction and defecation is affected. The defect in maternal care represents not only changes in the nutritional regime and insufficient supply of energetic, structural and regulatory substrates and molecules but also changes of complex stimulation field, affects on organism's integrity – its perception with an impact in the individual emotional sphere. The importance and effect of the deficiency of maternal behaviour in particular on the neuroendocrine, regulatory and integral mechanisms is of course variable. All the above mentioned functional effects do have a very specific set of structural correlates in the hippocampus, amygdala, prefrontal cortex or in the performance of receptors for e.g. oxytocin, leptin, insulin etc. (Viveros *et al* 2010; Chen *et al* 2009; Lukas *et al* 2010).

Very important is the fact, that the same factors influencing the laboratory rat females, i.e. insufficient or even absent maternal care, may continue their effects on the development of their own offspring.

We are then facing a sort of "pseudohereditability". This experimental model is nevertheless comparable to human society. The different (alternative) phenotype which by the virtue of mentioned deprivations or deviations was induced will have analogical effects on its own offspring generation. Exposition of pregnant female to e.g. inadequate stress can influence e.g. maturation processes in foster hippocampus etc. (Afadlal *et al* 2010).

There are not only possibilities but also real facts that unacquired features/functions might be in the same or

similar matter projected into following generations. Apart from that, there is an evidence that not only nutritional deprivation but also long term stress and another negative factors can increase the incidence and risk of cardiovascular, metabolic and even psychic disorders (schizophrenia) in the offspring generation (e.g. Reser 2007; Brixey *et al* 1993, etc.)

In the introduction of this paper the very pioneer papers were quoted intentionally; however they have been many times confirmed and enhanced methodologically by recent authors (e.g. Zhang *et al* 2004, 2010; Verhagen *et al* 2009; Ennis *et al* 2008; Rao *et al* 2010 etc.).

In the field of nutritional stress – deprivation from particular nutritional components – highly specific effects on the developing organism and its organ systems can be identified (e.g. vitamin A, vitamin B6, zinc, unsaturated fatty acids OMEGA-3 etc.). As an example, risk newborns show, among other things, significant deficit of PUFA-OMEGA-3 in blood serum. This fact represents an evident risk factor for development of e.g. immune system, higher risk of cardiovascular diseases, autoimmune diseases etc. (Mourek 2008; Mourek *et al* 2009). The question is to what extend the so called paramutations participate (Bernstein & Allis 2005; Resser 2007; Tsuang 2000).

The importance of maternal care, or its deficit respectively, on the development of newborns (particularly their neuroendocrine system) was stressed out.

This negative effect on the organism's maturation does not represent disability in longitudinal sense only (in the sense of retardation). It also represents a disability of the timing as well as the quality of maturation processes in the metabolic but also in structural-spatial sense.

Formation, tuning and maintenance of neuronal circuits in the brain

Qualitative differences in the integration function of the brain (intelligence and cognitive functions level, memory capacity) can be related to level of complexity of neuronal circuits in the cerebral cortex. Development of the nervous system is only partly genetically determined, significant effect have also factors of environment. However, it shows that those factors, besides acting directly (e.g., food availability), can also modulate the development and function of a structure by effecting gene transcription.

In the period of neuronal circuits' formation, the growth mode of axons and dendrites is given by the genetic program. It controls expression or specific components of cell membranes – neuronal adhesive proteins – which label the pathway and the target for growing processes. Adhesive proteins serve both as cell markers and receptors for reciprocal markers and they enable to form cell connections. Various types of those proteins are located at growing cones of axons and at dendrites and they were identified also at other locations of neuronal membranes. However, formation of cellular interactions is not the only function of adhesive proteins. They act as receptors linked to intracellular cascades regulating cellular functions including processes of gene activation, which is part of the mechanisms of axonal and dendritic proliferation (Ethell & Ethell 2007).

Surface markers for labelling pathway in neuronal and glial migration are exprimed only during the developmental phases. Such expression can be modulated by some cytokines and chomokines. For example in meningeal cells of lateral ventricles factor SDF-1 (stromal cell-derived factor-1) is exprimed. It attracts CXCR4 (specific ligand=receptor) of granule cells migrating from the subventricular germinal zone into the growing dentate gyrus during the late foetal and early postnatal development (Bagri at al 2002).

Optimal function of newly formed neuronal circuits is achieved gradually by tuning the structure according the actual functional load. During the CNS development more neurons (and their branches) are formed than necessary. Selective elimination (apoptosis) later on removes those neurons which did not form optimal functioning connections and they do not receive via their synaptic interactions the necessary amount of trophic factors. Similarly, some factors can increase number of axons and dendrites (*sprouting*) or conversely to reduce axon collaterals or dendritic branches if they were not properly wired (*pruning*) (Schafer & Stevens 2010). Neurotrophic factors (e.g., nerve growth factor – NGF and brain-derived growth factor – BDNF), are presumed to be responsible for structural tuning of neuronal circuits according to the functional load. Activity of the neurotrophic factors is controlled by cytokines (IL-1, IL-6, a TNF) (Frei *et al* 1989; Gadient *et al* 1990; Murphy *et al* 2000).

Given examples suggest that cytokines are important actors in the process of formation and remodelling of neuronal circuits. Cytokines were first described as molecules controlling the immune system. It is more and more evident that they mediate communication between cells of other systems too, nerve system including. Cytokines can affect the cell of origin (autocrine effect), surrounding cells (paracrine effect) or they can act after they reach the target tissue in the bloodstream (endocrine effect). Cytokines mostly belong to the glycozylated proteins and similarly to hormones they act after binding to specific receptors in cell membranes.

Cytokines play significant role not only in the described developmental plasticity but also in processes of adaptation and restoration plasticity – they mediate reaction to the functional load. Variations in the levels of some cytokines during the stress, in disease states, and after the nervous system integrity impairment have been repeatedly described. Cytokine level fluctuations (IL-1, IL-6, and TNF) are related to behavioural changes accompanying infectious diseases, malignan-

cies or injuries (e.g., sleep disorders, low appetite, body temperature changes, impairment of cognitive functions, low body activity, low libido, anhedonia) (Kronfol & Remick 2000; De La Garza 2005).

One of the frequent signs of diseased nerve system, memory dysfunction, was experimentally confirmed to be related to the level of cytokines. While low levels of cytokines IL-1 ("physiological level") improved in experiment the formation of memory traces, high cytokine level in animals during stress impaired the process of learning (Bianchi *et al* 1998). Even more negative effect on the formation of memory traces has the elevated level of IL-6, namely in elderly animals (Heyser *et al* 1997).

The role of cytokines in the mechanisms of nervous system plasticity has not been fully recognized yet. However, their role in the formation and tuning of neuronal circuits by means of environmental factors becomes evident. Undoubtedly they participate in the reactions to the changes of the functional load, which belong to pathogenic mechanisms during disease or injury of the nervous system. Changes in the cytokine level during the initial phase of brain impairment frequently have negative effects. In later stages they mostly act as mediators of recovery (Conrad *et al* 1999).

Heredity and plasticity

The progress and fate of a particular human subject depends on the interconnected effect of the basic genetic equipment and on the multiple factors of the environment in the broad sense of this concept, which may be active in different time relations and moreover it could be influenced by expected or unexpected changes in the area of genetic matrix as well as by the smaller or greater or even catastrophic events of the environment, which may change suddenly the demands of adaptation to an external environment to which the particular subject cannot adjust any more.

We may choose from the examples of genetic and at the same time dependent social consequences very sensitive models the observation of the effect of the particular form of the gene D4DR on the short arm of chromosome 11. This gene serves for transcription of the dopamine receptor, which is active in some regions of the brain. From a simplified point of view we may consider dopamine as the chemical substrate of motivation in the brain.

D4DR according to R. Ebstein (Ebstein & Belmaker 2000) contains in its middle structure the very changeable repetitive sequence, a minisatellite part long 48 letters, which is repeated 2 to 11 times. With majority of subjects there are present 4 to 7 copies, but some of them could have either less or more of these repetitions. The greater is the number of repeats, the less effective (sensitive) is dopamine receptor towards the ligation of the dopamine. In such a way we may talk about „long" and „short" version of gene.

Hamer (Hamer & Copeland 2000) measured in the group of 124 subjects divided according to the presence of long or short version of D4DR gene the tendency of subjects to seek „adventurous" events and than observe their D4DR genes. The subjects with one or two „ long" copies were seeking the changes and adventures significantly more than the subjects with two „short" copies. In this study the long genes were defined by presence of 6 or more minisatellite sequences. Hamer (Hamer & Copeland 2000) argued that the human subjects with long D4DR genes have low sensitivity to dopamine and therefore they need in their lives more intensive adventures and events to get the same „ dopamine highs" than the subjects with short genes, who get their satisfaction in an easier way from more common events of milder intensity. According to Hamer, the subjects with long D4DR genes could be called „the seekers of the change". In another study (Hamer & Copeland 2000) it was observed, that the heterosexual men with long gene D4DR have six times higher possibility to have intercourse with another man, than males with short genes and that homosexual men with long genes have the intercourse with females 5 times more probably than the homosexual men endowed with the short gene.

Hamer did not state that one particular gene only by itself would influence the drive for adventure and he concluded that effects of D4DR could explain not more than 4% of this personality feature and he expected that it is influenced by heredity from about 40% and there are existing more than ten further genes of the same effective variation which would reflect the variations of personality features in the population.

Correspondingly similar studies in which the authors tried to relate certain personality traits to certain genes were able to replicate the quoted observations, but there are critical studies also, which put these results into the question (Kritchevsky 2007; Link & Breaker 2009; Uher & McGuffin 2008). The discovery of genetic code of DNA showed the details of hereditary laws and supplemented the missing link in mechanisms of heredity and its realisation in the process of evolution which was sought in vain already by Darwin. This discovery reflected completely our intentions in the natural sciences to begin the process of exploration from the reductionist standpoint and to tend firmly at one given point of concept, in this case on the point of „Nature" in the opposition to the point of „Nurture". The first „position" explains in a better way the processes of long term evolution, the second one the evolution commanded by the necessity of quick adaptation to sudden and sometimes catastrophic changes of environment.

It seems, that living organisms, including the human subjects, have to their disposal formerly unknown mechanisms build in into their genetic system of replication, which enable them to react adaptively even to sudden and quick environmental change. To consider these mechanisms we must return to the hypothetical world of RNA which might pre-existed the evolution

dependent on DNA. During the unveiling of genetic code there appeared more and more clearly the fact, that there are much more genes and genetic material altogether and if we are speaking about 30.000 human genes, we are speaking about genes, coding proteins. These coding genes represent about 2 of genetic material only. The conclusion, that 98 of genetic code, called than „junk DNA" would be only some genetic rubbish the, the collection of non-functional archaic genes, fossils without any function and importance was with time less and less acceptable.

Indeed, geneticists have begun to observe the collection of „genes", which have clear function, even though they are not coding any protein, but are producing the RNA only. According to some geneticists, gene has been always defined in a too broad way and the appearance of genes, coding only by the way of RNA has increased misunderstanding, what the genes really are. Some of them are recommending to talk not so much about the gene, but to begin to call any segment, which could be transcribed into DNA as a „transcriptional unit". When we are looking into the world of RNA, we could see that RNA is capable to influence the metabolism of cell. Some transcripts in a similar way as proteins may react with other sequences of RNA, with DNA, with proteins and even with a small chemical compounds. The sequence of RNA may flow in the cytoplasm of the cell before it makes contact with other sequence of DNA or RNA, and it is joining with it and activate or inactivate it. The types of coding RNA could be different, from the type of „antisense RNA", the „microRNAs " which are short sequences of non-coding RNA, folded like hairpins and appearing in living organisms from plants to human beings. These short sequences of RNA seem to control the activity of many genes. Kritchevsky (Kosik & Kritchevsky 2005; Kritchevsky 2007) from Harvard University maintains, that short RNAs may have a very important role in the development of the brain (Rassoulzadegan *et al* 2006). The group of Ronald F.Beaker (Link & Breaker 2009) considered the question like many billions years before the appearance of DNA and proteins overlived RNA in the surrounding of the simplest forms of early life precursors. Beaker and others speculated that small „protoorganisms" needed to its overliving the RNA switches adapted to quick reactions to changes of environment and metabolism. Their laboratory produced successfully many „riboswitches", the units which at the same time are coding and non-coding particles.

When the RNA folds in, the non-coding end becomes the sensitive receptor for certain chemical target. The collision with such a target is inducing the switch and causes the other end of this particle, the coding end, which contains the matrix for protein to change its configuration and begins to produce the protein.

Few years ago this author with doc. Šerý and doc. Znojil in an unpublished lecture proposed that the prove of the above mentioned observation of the new possibilities brought about by RNA transcription gave new broad perspectives of the interactions of environment effects and the most inner metabolism of cells and organisms and are enlarging the adaptive possibilities of the „fatal" part of genome in living organisms, including humans with its less determined and possibly quickly changing part, which could give great advantage to their adaptive mechanisms and further limit the meaning of „nature – nurture contraversion".

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