Central noradrenergic hyperactivity early in life: a hypothesis on the origin of morpho-functional brain disorders induced by malnutrition

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Many studies have revealed that malnutrition, caused either by insufficient or unbalanced diet, during early stages of growth and development could result in a variety of morpho-functional brain disturbances, whose severity depends on the time of onset, duration and intensity of the nutritional injury. Nevertheless, little is known about the intimate mechanisms by which early malnutrition impairs brain structure and function. This article reviews evidence showing that (i) developmental malnutrition induces central noradrenergic hyperactivity, (ii) noradrenaline exerts a trophic role during brain development, and (iii) pharmacological reduction of central noradrenergic hyperactivity prevents malnutrition-induced functional brain disturbances.

Key terms: *brain development, clonidine, early malnutrition, noradrenaline, transcallosal evoked responses, visual evoked responses.*

A number of studies in humans (4, 12, 19, 39) and animals (13, 20, 25, 32, 33, 36, 41, 47, 55, 64, 73, 74) have revealed that inadequate nutrition –either in amount and/or in quality– during early stages of growth and development could result in a variety of behavioral and learning disturbances, the severity of these functional brain impairments being dependent on the time of onset, duration and intensity of the nutritional injury.

The deleterious effects of postnatal malnutrition on brain development have been largely investigated. Today, it is well known that malnutrition during lactation could alter brain structures that provide the anatomical, metabolic and functional substrate for the cognitive processes. In fact, neuroanatomical studies performed mainly in rats have shown that inadequate nutrition after birth results in alterations of the cerebral cortex such as decreased cortical thickness, reduced dendritic length, diminished number of dendritic spines, increased neuronal cell packing density, decreased synapse/neuron ratios and decreased rates of development of cortical pyramids determining the existence of dendritic fields of small dimensions (21, 23, 34, 35, 53, 69, 70, 72). Besides, electrophysiological studies utilizing direct electrical stimulation of cortical areas related to learning and behavior, such as the parietal association cortex and the prefrontal cortex, have revealed that postnatal malnutrition decreases cortical excitability and diminishes the ability of cortical neurons to follow repetitive stimulation (28, 45, 46, 52). These effects, which persist in adult animals, indicate functional alterations of the axodendritic synapses mediating direct cortical evoked responses. Further, it has been reported that malnutrition during the suckling period alters the

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developmental pattern of responses evoked in the prefrontal and parietal association cortices by stimulation of the locus coeruleus (58, 59). Other electrophysiological studies have revealed that postnatal malnutrition impairs in the rat the normal brain interhemispheric asymmetry of visual evoked responses and reduces the extent of the projecting field of transcallosal evoked responses (60, 61). In turn, neurochemical studies have shown that malnutrition during lactation results in increased noradrenaline concentration in whole brain (5) as well as in enhanced noradrenaline levels and release in the prefrontal and visual cortices (57, 59-61).

In summary, the above results indicate that inadequate nutrition after birth induces anatomical, electrophysiological and metabolic changes in the brain that could be related to the behavioral and learning disturbances found in postnatal malnutrition.

The effects of prenatal malnutrition on brain development have also been investigated. During the last two decades a number of studies in humans and animals have revealed that *in utero* malnutrition is related to low birth weight, high mortality rate and behavioral alterations (49). In fact, small-for-age children are more inclined than normal to suffer minimal brain dysfunction, characterized by behavioral disturbances, poor fine coordination and hyperreflexia (24). As in postnatal malnutrition, considerable efforts have been devoted to the study of the organic change induced in the brain by malnutrition during gestation. In this respect, it has been shown that small-for-age children, who died as a result of associated diseases, exhibited diminished brain cell number, as revealed by decreased brain DNA indexes (54), reduced brain lipids as revealed by diminished concentration of plasmalogens (38), decreased number of glial cells and altered dendritic development (49).

Studies carried out in rodents born from malnourished pregnant mothers have shown that they had poor adult learning performance, even if reared from birth by well-nourished dams (10, 41, 48, 66). Besides, research in animals has revealed that inadequate prepartum nutrition, such as severe food restriction to the mother, reduction of the protein content of the mother's diet, or clamping the uterine vessels of one horn, could induce body and brain weight deficits in the newborns (55, 14, 43, 62), as well as a variety of morpho-functional changes in their brains. In fact, morphometric and biochemical experimental studies have shown that inadequate prepartum nutrition induces brain deficits such as decrease of cell number, reduction of the protein content, decrease of glial proliferation and dendritic development (8, 51, 75, 76, 78, 79) and reduction of the corpus callosum size (68, 80). Besides, electrophysiological studies have revealed that nutritional restriction during gestation decreases cortical excitability (56), diminishes the spontaneous firing rate or cortical neurons (65), reduces the potentiation of excitatory postsynaptic potentials in the dentate gyrus (3), alters the efficacy of excitatory synaptic transmission at the level of the perforant path/dentate granule cell synapses (9), reduces the amplitude and field extension of transcallosal responses and abolishes the normal interhemispheric asymmetry of visual evoked responses (62). In turn, neurochemical studies have demonstrated that prenatal malnutrition results in increased concentration and release of noradrenaline (NA) in the brain of newborn pups (14, 50, 63). Further, it has been shown that intrauterine malnutrition induces abnormalities in the fatty acid content of neurons (40), decreases the myelin content of the forebrain (7) and reduces the Na-K-ATPase activity in the forebrain, cerebellum and hippocampus (15).

What does emerge from the foregoing data is that prenatal malnutrition may induce morpho-functional alterations in the brain.

As pointed out in the literature (42), prenatal malnutrition alters brain growth and development by affecting a variety of cellular processes, for example, by reducing the number of cells, by perturbing and desynchronizing cellular migration, by delaying or blocking cellular growth and differentiation, and by increasing cellular death. It is important to note that cellular processes, that are affected by prenatal malnutrition, in normal conditions are profoundly influenced by metabolic properties of the milieu. In fact, prior to synapse formation, monoamines may exert a paracrine role since they could serve as chemical signals participating in the

regulation of cellular events during early brain development such as neurogenesis, migration of neurons, differentiation and maturation of neurons, synaptogenesis, and even regression and programmed cellular death (29).

The issue that nutritional inadequacies during prenatal life increase central NA levels and enhance central NA release is of particular relevance, taking into account that central noradrenergic projections are an important regulator of normal regressive processes such as cell death, axonal pruning and synaptic elimination during synaptogenesis (6, 11, 44). These regressive processes appear to be characteristic of many brain regions; they occur during development and play a major role in establishing the structural and functional pattern of the adult central nervous system (16). The participation of the central NA system in regressive events has been demonstrated by studies showing that reduction of the amount of NA released in the brain, as a consequence of electrolytic lesions of the locus coeruleus or injections of 6-hydroxydopamine, induces abnormal increments in cortical synaptic density, in the number of dendrites of the cortical pyramidal cells and in the area occupied by commissural fibers in the dentate gyrus (2, 6, 37, 44, 71).

The above data suggest that the normal effect of noradrenergic innervation is of an inhibitory nature, limiting the formation of connections during brain development. It is likely that this noradrenergic regulatory mechanism starts very early, since, in the rat: (i) the cells that form the locus coeruleus undergo a period of intense mitotic activity between 11 and 13 days of gestation, after which cell division ceases (31); (ii) neurons storing NA are detectable in the brain as early as the 12th to 13th days of embryonic life (27); (iii) tyrosine hydroxylase and dopamine-beta-hydroxylase activities, indexes of functional maturation of noradrenergic

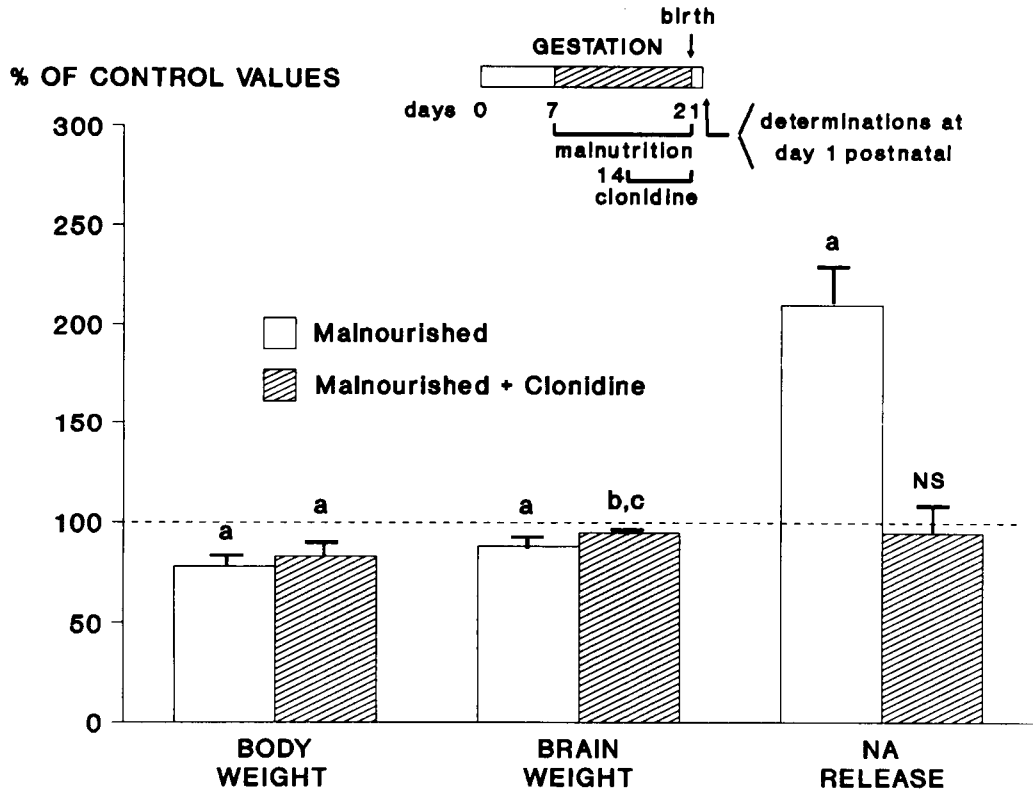

Fig 1. Changes induced by prenatal malnutrition on body weight, brain weight and visual cortex NA release. Clonidine treatment during gestation normalized NA release and partially prevented brain weight deficit. The drug did not improve or impair birth weight of malnourished pups. (Graphic representation summarizing data from references 62, 63). [a] $p < 0.005$; [b] $p < 0.05$, compared to controls; [c] $p < 0.025$ compared to malnourished pups without clonidine treatment. (Student's *t*-tests).

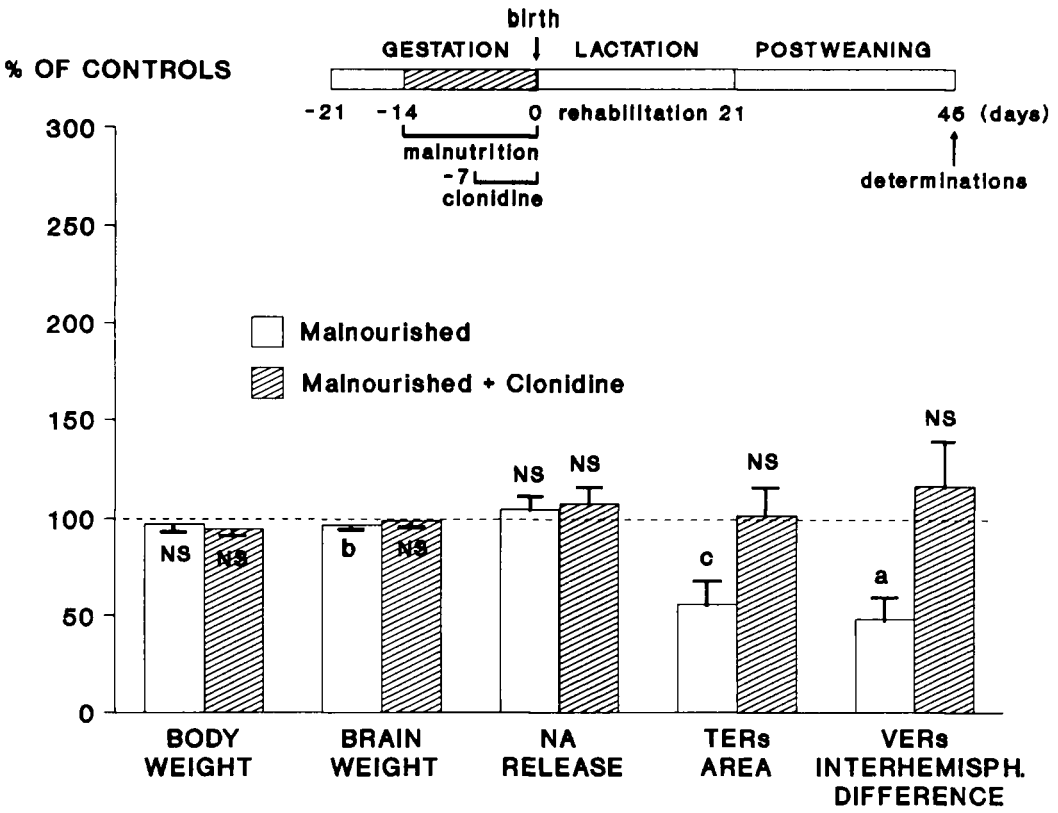

Fig 2. Clonidine treatment during gestation prevented long-term effects induced by prenatal malnutrition on brain weight, projecting field of transcallosal evoked responses and interhemispheric asymmetry of visual evoked responses of the progeny. (Graphic representation summarizing data from references 62, 63). [a] $p < 0.01$; [b] $p < 0.025$; [c] $p < 0.05$, in relation to controls (Student's *t*-tests).

neurons, have been demonstrated in the brain of fetal rats at 15 days of gestation (17, 18); and (iv) cortical synapses have been observed at day 16 postconception (77). From these studies it is apparent that in the rat the noradrenergic system is "operative" by the end of gestation and, therefore, could be influenced as early as the fetal life by stressors such as nutritional, environmental, etc.

The facts that prenatal malnutrition increases central NA activity and that NA participates in the normal development of the brain, lead to the hypothesis that some of the modifications induced by nutritional injuries on brain structures could be due, at least in part, to the high activity of central NA which in turn can disrupt normal brain cellular events. If so, pharmacological reduction of the central NA activity during development should prevent some of the brain disorders induced by prenatal malnutrition. This idea finds support in studies performed in rats that were malnourished during gestation by restricting laboratory chow to their mothers (10 g daily) from day 8 postconception until parturition. Results of these studies (Fig 1) showed that pups submitted to this form of prenatal malnutrition exhibited at birth significant deficits in body and brain weights as well as a significant increase of NA release in the visual cortex (62, 63). Besides, at adulthood (Fig 2) these animals showed significant deficits in the projecting field of transcallosal evoked responses (62, 63). As it is known, the corpus callosum is the main pathway of cerebral interhemispheric communication and undergo important normal regressive processes during early development (30) that could be magnified by the enhanced central NA activity.

Clonidine administration to food-restricted pregnant mothers (Figs 1 and 2), from day 14 postconception to parturition, prevented in the progeny looses in interhemispheric asymmetry of visual evoked responses and deficits of projecting field of transcallosal evoked

responses (63). As it is known, clonidine reduces the release of central NA by activating presynaptic inhibitory α2 adrenoceptors. Thus, the preventive effect of clonidine on brain deficits induced by prenatal malnutrition could be attributable to the early reduction of the increased NA overflow and, consequently, to a normalization of noradrenergic mechanisms regulating regressive events. The possibility must be considered that other clonidine-sensitive neurotransmitter systems could also be responsible for the effects observed. In fact, it has been shown that α-adrenoceptors may also participate in regulating the release of central neurotransmitters other than NA, including serotonin (26), acetylcholine (67) and glutamate (22). Nevertheless, this alternative appears as unlikely on the basis of recent studies showing that reduction of prenatal malnutrition-induced NA hyperactivity by utilizing α-methyl-p-tyrosine, an inhibitor of tyrosine hydroxylase, can also prevent functional deficits of interhemispheric connectivity as well as abolition of interhemispheric asymmetry of visual evoked responses (1).

In light of the above data, it is apparent that a suitable amount of central NA released in the milieu during development is required to assure an adequate organization of the brain. As previously mentioned, severe reduction of brain NA activity resulting from lesions of the central NA system leads to abnormal increments in dendritic/axonal branching, whereas the increase of brain NA activity consecutive to malnutrition could lead to an opposite effect. In this context, the developing brain is susceptible to be affected by nutritional and environmental stressors, that alter the milieu, as early as the fetal life.

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