

available at www.sciencedirect.comwww.elsevier.com/locate/brainres**BRAIN
RESEARCH****Research Report****Developmental changes in content of glial marker proteins in rats exposed to protein malnutrition**

Ana Maria Feoli^{a,b}, Marina C. Leite^a, Ana Carolina Tramontina^a, Francine Tramontina^a,
Thais Posser^c, Letícia Rodrigues^d, Alessandra Swarowsky^d, André Quincozes-Santos^a,
Rodrigo B. Leal^c, Carmem Gottfried^a, Marcos Luiz Perry^a, Carlos-Alberto Gonçalves^{a,d,*}

^aDepartamento de Bioquímica, ICBS, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

^bFaculdade de Enfermagem, Nutrição e Fisioterapia, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil

^cDepartamento de Bioquímica, CCB, Universidade Federal de Santa Catarina, Florianópolis, Brazil

^dPrograma de Pós-Graduação em Neurociências, ICBS, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

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ABSTRACT

Pre- and postnatal protein malnutrition (PMN) adversely affects the developing brain in numerous ways, but only a few studies have investigated specific glial parameters. This study aimed to evaluate specific glial changes of rats exposed to pre and postnatal PMN, based on glial fibrillary acidic protein (GFAP) and S100B immunoccontents as well as glutamine synthetase (GS), in cerebral cortex, hippocampus, cerebellum and cerebrospinal fluid, on the 2nd, 15th and 60th postnatal days. We found increases in GFAP, S100B and GS in the cerebral cortex at birth, suggesting an astrogliosis. Hippocampus and cerebellum also exhibited this profile at birth. However, a significant interaction between age and diet in postnatal life was observed only in the S100B of the cerebral cortex. No changes in the content of GFAP and S100B and GS activity were found on the 60th postnatal day in malnourished rats. In contrast, following an increase in the levels of S100B in the cerebrospinal fluid, during the early developmental stages, levels remained elevated on the 60th postnatal day. Our data support the concept of astrogliosis at birth, induced by PMN, and involve extracellular-regulated kinase activation. Specific alterations in cerebral cortex emphasize the regional vulnerability of the brain to malnutrition; some alterations were observed only at birth (e.g. GFAP); others were observed on the 2nd and 15th post-natal days (e.g. ERK phosphorylation). Taken together, transient and persistent alterations (e.g. elevated extracellular levels of S100B) suggest some brain damage or a risk of brain diseases in rats exposed to PMN.

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1. Introduction

Malnutrition is an important and very common insult to human brain development and function. The global prevalence of stunting in <5-year-old children associated with

undernourishment, particularly protein restriction, is increasing despite the decline in childhood mortality (Caballero, 2002). Prenatal and early postnatal protein malnutrition (PMN) adversely affects the developing brain in numerous ways, depending largely on its timing in relation to various develop-

* Corresponding author. Departamento de Bioquímica, ICBS, Universidade Federal do Rio Grande do Sul, Ramiro Barcelos, 2600-Anexo, 90035-003, Porto Alegre, RS, Brazil.

E-mail address: casg@ufrgs.br (C.-A. Gonçalves).

mental events in the brain and, to a lesser extent, on the type and severity of the deprivation (Morgane et al., 1993).

Several studies have shown biochemical changes in the central nervous system (CNS) in experimental models of PMN, particularly involving specific neurotransmitter systems (Morgane et al., 2002; Steiger et al., 2003; Wiggins et al., 1984; Rocha and Souza, 1994). More recently, we have shown changes in the neurotransmission mediated by glutamate, the main excitatory neurotransmitter in the CNS (Rotta et al., 2003). Glial cells, particularly astrocytes, are involved in the metabolic support of neurons, glutamate uptake, synthesis of glutamine, secretion of neurotrophic factors and antioxidant defense (Takuma et al., 2004). Surprisingly, only a few studies have investigated specific glial parameters (Clos et al., 1982; Giuffrida et al., 1980; Gressens et al., 1997), despite growing evidence of the importance of glial cells for neuronal development, survival and plasticity. In fact, during CNS development, the generation of cell types occurs sequentially, and neurons are predominantly generated before glial cells (Sauvageot and Stiles, 2002). Precocious or delayed glial differentiation may cause severe disorganization and dysfunction of the CNS (He et al., 2005).

Glial fibrillary acidic protein (GFAP) is a specific marker of mature astrocytes. CNS injuries are commonly accompanied by astrogliosis, characterized by an increase in GFAP (O'Callaghan, 1991). On the other hand, reduction of GFAP during prenatal development induced by protein restriction has been associated with delayed astrocytogenesis (Giuffrida et al., 1980). S100B protein is another useful marker of brain injury, expressed and secreted by astrocytes (Donato, 2001) and a lower content of S100 protein (possibly S100B) has been found in the cerebellum of malnourished rats (Clos et al., 1982). We have previously demonstrated brain oxidative stress in malnourished rats (Feoli et al., 2006a,b), suggesting a glial alteration in this kind of insult.

The present study aimed to evaluate astrocytic changes in different brain regions during pre- and postnatal developmental periods in response to protein malnourishment. In order to address this issue, specific markers – GFAP and S100B immunoreactivity and glutamine synthetase activity – were analysed on the 2nd, 15th and 60th postnatal days in the cerebral cortex, hippocampus and cerebellum of normal and protein malnourished rats. S100B content in cerebrospinal fluid was also measured on the 21st and 60th postnatal days.

2. Results

Rats were submitted to prenatal and postnatal PMN. The severity of the PMN model in the postnatal development was evaluated by measuring the body and brain weight on the 2nd, 15th and 60th postnatal days (Fig. 1). There was a significant effect of age ($p < 10^{-4}$, $F_{(2, 53)} = 335.54$) and diet ($p < 10^{-4}$, $F_{(1, 53)} = 46.30$) on brain weight, as well as a significant interaction between age–diet ($p < 10^{-4}$, $F_{(2, 53)} = 23.95$). With regard to body weight, we also observed an effect dependent on age ($p < 10^{-4}$, $F_{(2, 42)} = 693.70$) or diet ($p < 10^{-4}$, $F_{(1, 42)} = 142.96$) and a significant interaction between age and diet ($p < 10^{-4}$, $F_{(2, 42)} = 88.51$).

The brain weight and glial protein parameters on the 2nd postnatal day depict the final representation of the prenatal PMN insult at birth; we found a significant decrease in the

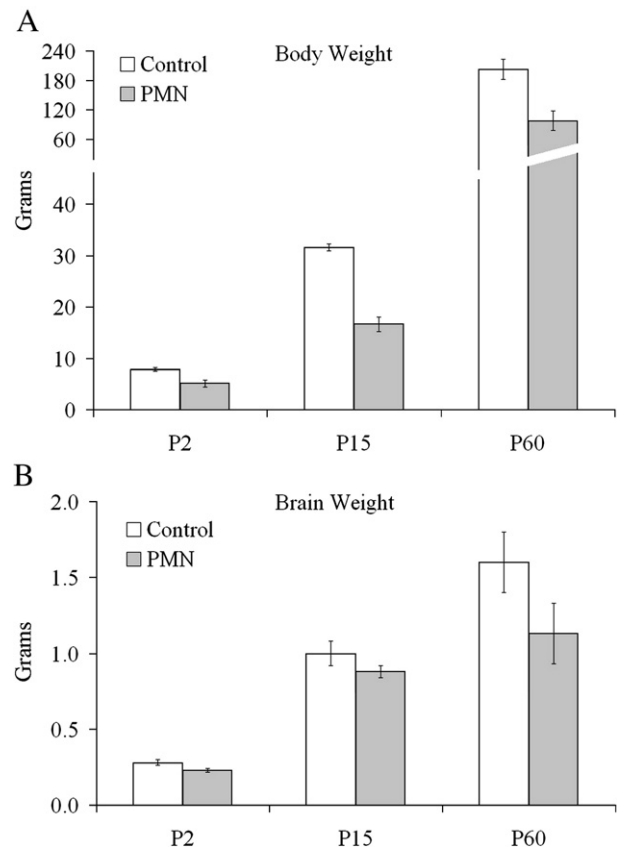


Fig. 1 – Post-natal development profile of body and brain weight of rats exposed to PMN. Rats were exposed to a 7% protein diet during pre- and postnatal life. Weights were measured on the 2nd (P2), 15th (P15) and 60th (P60) postnatal days. Values are mean $\pm$ standard error of 6–8 rats in each group. Significant effects, dependent on age or diet, were observed (two-way ANOVA, $p < 0.05$).

brain tissue, accompanied by an increase in glial proteins in all brain structures analysed (Table 2, Student's *t* test). A qualitative analysis of the cerebral cortex on the 2nd postnatal day, employing immunohistochemical staining for GFAP, confirmed that GFAP-positive cells are apparently more immunostained in malnourished rats (Fig. 2B). However, this scenario changed when mean values from the 15th and 60th postnatal days were added to analyze postnatal development (by two-way ANOVA).

The effect of age on GFAP content was observed in all brain structures, in both normal and malnourished animals (Figs. 2A, C and D). In cerebral cortex, the effect of age was significant ($p < 10^{-4}$, $F_{(2, 40)} = 37.34$), but no significant effect of diet was observed ($p = 0.225$, $F_{(1, 40)} = 1.52$); no age–diet interaction was found ($p = 0.64$, $F_{(2, 40)} = 0.450$). Similarly, the effect of age was significant ($p < 10^{-4}$) on GFAP content of hippocampus and cerebellum ($F_{(2, 41)} = 25.47$ and $F_{(2, 31)} = 145.88$, respectively) with no effect of diet ($p = 0.334$, $F_{(1, 41)} = 0.918$ and $p = 0.917$, $F_{(1, 31)} = 0.011$, for hippocampus and cerebellum, respectively). No interaction (age–diet) was observed in the hippocampus and cerebellum ($p = 0.283$, $F_{(2, 41)} = 1.30$ and $p = 0.543$, $F_{(2, 31)} = 0.622$, respectively).

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