

Fig. 11. Sections at the level of the cerebellum. IMPACT immunoreactivity in the mouse (A), rat (D), and marmoset (F), and insets shown in higher magnification in B,C,E,G, respectively, with the Purkinje cell layer indicated with black arrowheads and cells with morphological features of GABAergic interneurons in the granular layer indicated with arrows. In the mouse and rat cerebellum Pur-

kinje cells with no detectable IMPACT expression are indicated with asterisks. IMPACT-positive cells in the molecular layer are indicated with a white arrowhead in E. Gr, granular layer; Mol, molecular layer; Pk, Purkinje cell layer; Wm, white matter. Scale bars = 100  $\mu$ m in A,E,G; 50  $\mu$ m in B,C; 300  $\mu$ m in D,F.

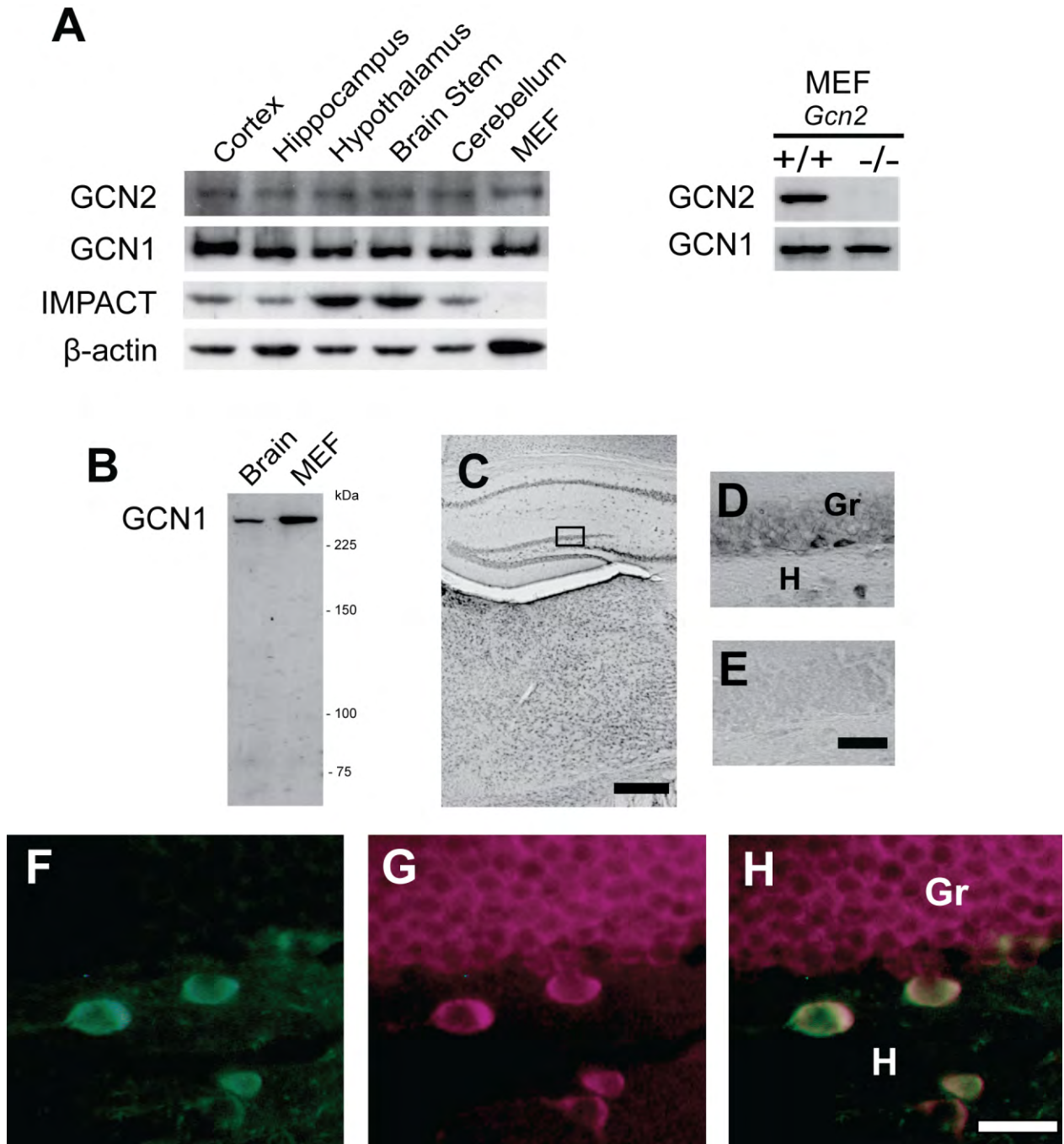


Fig. 12. GCN1 and GCN2 expression in the mouse brain. **A:** Left panel: immunoblots of extracts of the indicated brain areas and of mouse embryonic fibroblasts (MEF) (10  $\mu$ g total protein). GCN2 and GCN1 blots were performed in the same membrane from samples subjected to 7% SDS-PAGE; identical samples were subjected, in parallel, to a 12% SDS-PAGE and used for immunoblots with antibodies against IMPACT and  $\beta$ -actin. Right panel: immunoblot of MEFs derived from wildtype and *Gcn2*<sup>-/-</sup> mice employing antibodies against GCN2; the same membrane was incubated with anti-GCN1 serum for normalization. **B:** Immunoblot of brain and MEF extracts with anti-GCN1 affinity-purified antibodies; molecular mass stan-

dards (kDa) are indicated. **C:** Immunohistochemistry of a section of the mouse brain using anti-GCN1 affinity-purified antibodies, with the inset shown at higher magnification in **D**. **E:** Immunohistochemistry of the same area shown in **D** using anti-GCN1 antibodies previously incubated with the purified recombinant His6-GCN1<sup>2204-2651</sup> protein. **F,G:** Double labeling immunofluorescence of the hippocampal dentate gyrus/granule cell layer using guinea pig anti-IMPACT antibodies (green) and rabbit anti-GCN1 antibodies (red); the merged image is shown in the panel on the right (**F**). Scale bars = 200  $\mu$ m in **B,C**; 20  $\mu$ m in **D-G**.



## Learning and memory (hippocampus and amygdala)

In the hippocampus, IMPACT was conspicuously absent in dentate granule cells and was expressed at very low levels in CA1, CA2, and CA3 pyramidal cells, while intensely staining hilar and other interneurons. GCN2 has been reported to be required for the induction of long-term potentiation (LTP) in the CA1 area of the hippocampus (Costa-Mattioli et al., 2005). *Gcn2*<sup>-/-</sup> animals displayed increased early LTP (E-LTP) and a defective late LTP (L-LTP) in slices of the hippocampus submitted to one train of electric stimulation that in the wildtype animals lead to L-LTP. This was reflected in increased hippocampal-dependent memory upon weak training, but defective upon intense training. Thus, activation of GCN2 is intrinsically related to the transformation of E-LTP to L-LTP. Our observations of low IMPACT levels in the pyramidal cells of CA1 are thus in agreement with the electrophysiology and behavioral data. The low levels of IMPACT in the neuronal populations where LTP was analyzed (CA1) is consistent with GCN2 activation. The hippocampal inhibitory interneurons, which display high levels of IMPACT, control the excitability and synchronization of projection cells (Buzsaki and Chrobak, 1995; Freund and Buzsaki, 1996; Chapman and Lacaille, 1999). We hypothesize that the high expression levels of IMPACT in hippocampal interneurons, with the resulting inhibition of GCN2 and therefore of ATF4 expression, might contribute to the differences in the long-term synaptic plasticity among this neuronal population, relative to that of the granule and pyramidal cells.

In the amygdaloid complex the lateral amygdaloid and intercalated nuclei were devoid of IMPACT, in contrast to other nuclei in this region. The lateral amygdala is a key component of the neural system involved in emotional learning and memory, and is essential for formation of memory during fear conditioning especially when auditory stimulus is used (Rodrigues et al., 2004). The study of GCN2 knockout animals indicated that fear conditioning by auditory stimulus was not impaired. This is in agreement with evidence that the biochemical pathways involved in hippocampal and amygdala LTP are not the same. A critical role for phosphatidylinositol 3-kinase (PI3K) in fear conditioning in the amygdala has been shown (Lin et al., 2001). Thus, contrary to the hippocampus, the lack of IMPACT in the lateral amygdala does not relate to a need for GCN2 in LTP in these neurons. Indeed, it has been suggested that either GCN2 is not the major eIF2 $\alpha$  kinase in the amygdala or the pathway that turns off GCN2 activity is not activated in some forms of amygdala-dependent learning (Costa-Mattioli et al., 2007).

## Circadian and theta rhythms

In contrast to most thalamic nuclei, which lack IMPACT staining, the intergeniculate leaf (IGL) has a high abundance of very intensely IMPACT-stained neurons. The IGL, along with the hypothalamic suprachiasmatic nucleus (SCN), are the major circadian rhythm generators. The SCN, although not an exception to the high levels of IMPACT found in the hypothalamus, had the highest percentage of very high IMPACT-expressing neurons in all the brain. The IGL is involved in both photic and nonphotic effects on the circadian rhythm, and projects

directly to the SCN. Other nuclei in the thalamus that had intense IMPACT staining, clearly above other nuclei in the region, include those that are interconnected with the IGL and involved in circadian rhythms/sleep-wake cycles: the paraventricular nucleus, the ventral lateral geniculate nucleus, medial thalamic nuclei, ventral reuniens, and reticular nucleus. Nucleus reuniens also differed from almost all other thalamic nuclei, given its high expression levels of IMPACT, in the rodent brains. Together with the septum and the vertical limb of the diagonal band, all of which also had very high levels of IMPACT, nucleus reuniens is important for the generation of the hippocampal theta rhythm (Vertes and Kocsis, 1997). Circadian variation of theta activity during wakefulness may correspond to the circadian variation in sleep propensity (Aeschbach et al., 1997). The reticular nucleus, another exception in the general pattern of lack of IMPACT in thalamic nuclei, is exclusively comprised of GABAergic inhibitory neurons that solely project to other thalamic neurons, thus regulating their activity (for a review, see Steriade, 2001). As with the SCN, the reticular thalamus has been demonstrated to participate in sleep-wake cycles.

A number of other brain structures are readily associated with the sleep-wake cycle: the basal forebrain, posterior hypothalamus, lateral hypothalamus, ventrolateral, locus ceruleus, raphe nucleus, peduncolopontine nucleus, and nucleus pontis oralis (España and Scammell, 2004; Saper et al., 2005; Steriade, 2005). Among all of these different structures there was one notable exception with regard to the pattern of IMPACT staining. The nucleus pontis oralis had absolutely no IMPACT staining in any of the three species, contrasting with other pontine structures.

From this picture, IMPACT seems to emerge as somehow associated with the firing patterns of neurons.

## Rodents versus primate

A few neuronal groups showed marked differences in IMPACT expression between rodents and marmoset. These were: neurons in the hippocampal hilus, the nucleus reuniens, and zona incerta, all showing less IMPACT in marmoset than in mouse or rat; the Purkinje cells, which were much more strongly labeled in the marmoset; and the distribution of IMPACT-positive neurons in the neocortex, restricted to layer V in the marmoset. It should be emphasized here that the lower expression of IMPACT observed in the marmoset in the first case was based on the levels of labeling observed for other structures in the same sections or in sections processed in parallel. These observations were thus not influenced by the specificity of the antibodies. The strong labeling of the Purkinje cells in the marmoset was also ascertained by the inclusion of other brain sections in the same immunohistochemistry reaction.

## CONCLUSION

Most neuronal markers are able to characterize a given brain area by means of an aspect associated with neurotransmission. The basic biochemical machinery only rarely has been found to discriminate any given neuronal group. The data shown here provide evidence for the differential expression in specific neuronal groups of a protein that is evolutionarily highly conserved and critically involved in translational regulation, IMPACT.

Given the currently available data on IMPACT expression in neurons and its evident heterogeneous expression in different brain areas, we can only speculate on its possible relevance in neurophysiology. Here we advanced the hypothesis that high IMPACT expression levels may be associated with rather stereotyped neuronal firing patterns. Given the association between IMPACT and eIF2 $\alpha$  phosphorylation (Pereira et al., 2005), and thus in protein synthesis, we suggest that the presence or absence of IMPACT might contribute to define how neurons regulate synaptic plasticity and thus maintain or alter their connectivity in light of environmental changes. On this issue neurons can be divided into two broad groups: with homeostatic plasticity or with Hebbian plasticity (Miller, 1996; Turrigiano and Nelson, 2004). While Hebbian plasticity underlies mechanisms of long-term potentiation and long-term depression, homeostatic mechanisms promote stability, preventing neural circuits from becoming hyper- or hypoactive. In this perspective, a neuron can control changes in other neurons, while itself remaining responsive without a change. Thus, high levels of IMPACT might be associated with the relative resistance of neurons to plastic changes. Thus, we speculate that neurons where IMPACT is overexpressed will show resistance to GCN2 activation induced by neuronal activity or by physiological stresses, and therefore no increase in ATF4 protein levels will result. As a consequence, no downstream signaling will be activated, contributing to maintaining the homeostasis of the neuronal circuitry. As a whole, the hypothalamic and brainstem neurons would require this homeostatic mechanism for maintaining constant control of body functions.

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*Se um autor faz você voltar atrás na leitura, seja de um período ou de uma simples frase, não o julgue profundo demais, não fique complexado: o inferior é ele.*

*Mário Quintana*



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