Hepatic encephalopathy (HE) is a multifaceted disorder, costing the US in excess of $7 billion a year to treat, and is caused by liver toxicity, cirrhosis, multiple acquired portosystemic shunts, and congenital portosystemic shunts. Several substances reach toxic levels in the blood of HE patients, but hyperammonemia (HA) is one of the main contributing factors to the neurological disturbances that affect astrocytes of the central nervous system (CNS), such as ataxia, seizures, coma and death. Astrocytes are key components of the blood-brain-barrier, in partnership with endothelial cells, and both of these cell types are putative target cells for C-type natriuretic peptide (CNP), the major natriuretic peptide of the CNS. However, the relationship between CNP and HA is currently unknown. In this study, we examined the expression and pharmacological control of CNP in rat C6 glioma cells (used as model astrocytes), in the presence of hyperammonemia. Cells were cultured in the absence and presence of pathological concentrations of ammonium chloride (NH_4Cl, an ammonia donor), to mimic chronic and acute HA conditions. Multiplex RT-qPCR was performed on extracted total RNA, to determine the effects of HA on astrocyte gene transcription. Extracellular and total cGMP determinations were made using a cGMP enzyme immunoassay, to determine the effect of HA on cGMP accumulation and cGMP efflux. Phase-contrast microscopy was performed to examine changes in cell morphology under conditions of HA. Multiplex RTqPCR revealed the presence of all three natriuretic peptide genes *(Nppa, Nppb, Nppc*) and their receptors (*Npr1, Npr2, Npr3*) in C6 glioma cells. However, CNP, but not ANP, caused a significant increase in total cGMP accumulation, suggesting that C6 cells express functional guanylyl cyclase-B (GC-B/*Npr2*) receptors. When C6 cells were pre-treated with 10mM NH_4Cl for 1h ('acute' HA) or 24h ('chronic' HA), there were significant reductions in CNP-stimulated cGMP accumulation, indicative of heterologous desensitization and down-regulation (to 65.2±11.0% (*P<0.05) and 66.2±5.0% (**P<0.01), after 1h and 24h, respectively). Furthermore, when cGMP efflux was determined in cells treated without or with CNP in the absence or presence of HA, the presence of ammonia caused a dramatic inhibition in the concentration of extracellular cGMP (****P<0.001, after 48h and 72h). Subsequent multiplex RT-qPCR demonstrated expression of multi drug resistance proteins 4 and 5 (*Mrp4, Mrp5*) which were sensitive to CNP and HA treatment. Finally, C6 cells subjected to chronic HA conditions exhibited abnormal morphology compared with control cells, but these changes were prevented by the presence of CNP. Collectively, these data demonstrate functional interaction between CNP signalling and HA in model astrocytes.