Following cardiac transplantation, the secretion of the cardiac-derived natriuretic peptides (NPs) atrial natriuretic factor (ANF) and brain natriuretic peptide (BNP) are significantly elevated despite normalization of hemodynamic and neuroendocrine parameters. Discoordinate increases in BNP plasma levels coincident with allograft rejection suggest that pro-inflammatory cytokines may selectively modulate NP gene expression and secretion from the endocrine heart. We investigated if individual recombinant pro-inflammatory cytokines or conditioned medium derived from an allogenic mixed lymphocyte reaction (MLR) can upregulate NP gene expression and secretion from neonatal rat ventricular cardiocyte cultures. Incubation with IL-1β (0.5 to 10 ng/ml) or TNF-α (0.5 to 20 ng/ml) elicited a dose and time dependent significant increase in BNP mRNA and secretion (p<0.001), whereas neither ANF mRNA nor secretion was affected by treatment. Furthermore, IL-1β and TNF-α significantly activated a transiently transfected rat −2.2 kb BNP promoter. Inhibition of p38 MAP kinase with SB203580 abolished both IL-1β and TNF-α stimulated BNP gene expression and release. SB203580 treatment also inhibited IL-1β and TNF-α activation of the rat −2.2 kb BNP promoter. Other pro-inflammatory and immunoregulatory cytokines like IL-6, IL-2 and IFN-γ did not alter either BNP or ANF secretion. The allogenic MLR is an in-vitro model of transplantation immunity and conditioned medium from these cultures was used in order to circumvent the omission of individual cytokines or their combination. MLR conditioned medium in 10, 20, 50 and 100% proportions increased BNP but not ANF secretion with respect to the basal lymphocyte medium control in 10, 20, 50 and 100% proportions. These results suggest that individual pro-inflammatory cytokines as well as substances from a specific immunogenic reaction can selectively upregulate BNP expression from the endocrine heart.