Nuclear protein post-translational modifications, such as acetylation, methylation and ubiquitination (Ubq) are important epigenetic mechanisms involved in synaptic plasticity and memory formation (1). Among these, Ubq has been shown to be involved in the regulation of many cellular processes including protein degradation and gene expression regulation. Despite many years of intensive research, the knowledge of global Ubq event remains poorly characterized. Accumulating evidence indicates that the Ubq-proteasome system (UPS) is the primary proteolytic complex specialized in the targeted degradation of Ubq-proteins which are recognized by the 26S proteasome. The 26S proteasome consists of two main structures: the core particle (20S-CP consisting of α/β heptameric rings) responsible for protein hydrolysis, and the regulatory particle (19S-RP) organized in 'lid' and 'base' sections (2). Recent evidence reports a role for the UPS in activity-dependent synaptic remodeling, such as memory formation after cocaine exposure (3). Moreover, proteasome inhibition has been associated with chronic ethanol (EtOH) exposure, since EtOH promotes the accumulation of oxidatively damaged histones (4). The aim of the study was to evaluate the effect on proteasome activity induced by the exposure of SH-SY5Y neuroblastoma cells to cocaine or EtOH. In addition, gene expression changes of selected genes encoding for specific proteasome subunits, caused by cocaine or EtOH exposure were investigated. To this purpose, cells were treated with 5µM cocaine or 40mM ethanol for different time intervals: 2h, 24h, and 48h. Results showed an opposite modulation of proteasome activity induced by cocaine and ethanol after 2h. Indeed, cocaine increased 20S activity (131±10.63 vs. control 100±4.54; p<0.01) whereas ethanol induced a significant reduction (86±1.96 vs. control 100±2.85, p<0.05). Subsequently, we analyzed the mRNA levels of specific 26S proteasome subunits. The ß1 and ß2 subunits were up-regulated by treatments. Indeed, cocaine increased ß1 gene expression after 2h (1.50±0.07 vs. control 1±0.04, p<0.001) and ethanol induced similar alterations in ß1 and ß2 subunits. In particular, after EtOH the ß1 subunit gene expression was up-regulated at 2 and 24h (1.59±0.05 vs. control 1±0.04; 2.01±0.12 vs. control 1±0.07, p<0.001 respectively) and ß2 mRNA levels increased after 24h (1.28±0.03 vs. control 1±0.07, p<0.01). Regarding the α subunits, cocaine caused a down-regulation of α5 gene expression at 24h (0.59±0.05 vs. control 1±0.04, p<0.05), followed by up-regulation after 48h (1.35±0.07 vs. control 1±0.08, p<0.05). A similar trend was observed for α6 mRNA levels, which were down-regulated after 2h and 24h (0.41±0.05 vs. control 1±0.06; 0.38±0.04 vs. control 1±0.06, p<0.001, respectively), and up-regulated after 48h (1.38±0.04 vs. control 1±0.08, p<0.001) by cocaine. In contrast, ethanol increased α5 gene expression after 2h (1.55±0.11 vs. control 1±0.07, p<0.001) and 48h (1.49±0.15 vs. control 1±0.08, p<0.01). Moreover, we observed that the Rpt3 subunit was strongly up-regulated by cocaine at 2h and 24h (1.48±0.06 vs. control 1±0.05; 3.87±0.07 vs. control 1±0.06, p<0.001, respectively). Conversely, ethanol exposure induced a marked down-regulation after 2h (0.59±0.09 vs. control 1±0.05, p<0.01). Results indicate that ethanol and cocaine differently affect the 26S proteasome activity. The alteration was drug-specific, since cocaine increased and ethanol reduced proteolytic activity. Moreover, the alterations of subunit gene expression here observed suggest the hypothesis that these two addictive drugs, despite displaying different mechanisms of action, may share the 26S-proteasome machinery as a common molecular target.