ABSTRACT

Polyamines are small polycationic molecules present in all organisms whose essential functions are not yet completely understood. On the other hand, high concentrations of polyamines are toxic through mechanisms also unknown (Alejandro *et al*., 2007, EMBO J). The objective of this work was to elucidate the toxicity mechanisms of norespermidine (NE), an uncommon triamine which is not present in the majority of studied organisms, by studying its toxic effect in *Arabidopsis thaliana*, *Saccharomyces cerevisiae* and *HeLa* human cell lines. Preliminary results showed that this substance incudes response genes to oxidative, osmotic and heat shock stress. This observations led us to evaluate the effect of NE at the level of polyubicuitylated proteins, where we demonstrated that this substance reduces the levels of this proteins, most probably via an inhibition of the polyubicuitylation cascade. Recently Suraweera *et al*., (2012, Mol Cell) observed that proteasomal inhibition caused a lethal depletion of intracellular amino acids, and that supplementation of amino acids restored normal growth. Similarly, we've demonstrated that NE treatment induces the GCN pathway, a signal transduction pathway which gets activated in the absence of amino acids, and that supplementation with amino acids confers tolerance to NE. In addition, there are several evidences that hint that NE could also be inhibiting the TOR1 complex pathway, another signal transducing cascade that responds to amino acids. Taken together, all this data suggests that NE, by inhibiting polyubicuitylation, has a similar effect to other proteasomal inhibitors, causing an intracellular lethal depletion of amino acids. Furthermore, we observed that espermidine, a natural triamine in the organisms studied, has a similar effect at high concentracions as the NE. Finally, we've studied the effect of these substances promoting yeast lifespan and the possible implication of the GCN and TOR1 pathways.