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Meeting abstract

Selective serotonin reuptake inhibitors induce cell death via the unfolded protein response

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Selective serotonin reuptake inhibitors (SSRIs) have been observed to drive programmed cell death in Burkitt lymphoma cells. Further studies, however, showed that SSRIs induce apoptosis with little, if any, appreciable selectivity. Actually, the selectivity appears to be so low that SSRIs can kill protozoa such as *Trichomonas vaginalis*. Although the serotonin transporter SERT was initially considered as SSRI target in inducing programmed cell death, this concept has been rejected repeatedly. N-acetylated versions of SSRIs, which are not capable of inhibiting serotonin reuptake anymore, were shown to kill cells in concentration ranges comparable to those of their non-acetylated original versions. Our working hypothesis is that SSRIs induce cell death via activation of the endoplasmic reticulum stress response/unfolded protein response (UPR). To address this hypothesis, we performed a luciferase reporter assay (in HEK293 and HeLa cells), in which the firefly luciferase gene is under the control of the promoter for glucose-regulated protein of 78 kD (GRP78), an endoplasmic reticulum (ER) chaperone mainly expressed during the UPR. Several SSRIs (paroxetine, fluvoxamine, fluoxetine and citalopram) and their N-acetylated versions induce GRP78 expression with steep concentration-response curves, comparable to those obtained for killing cells. SSRIs also trigger activation of caspase 3/7, as observed with a caspase 3/7-dependent fluorescent substrate, and expression of the endoplasmic reticulum stress protein C/EBP-homologous protein (CHOP-10). Our results suggest that SSRIs induce cell death via the UPR, and further experiments are designed to strengthen our hypothesis. We will also investigate, if this effect is conserved throughout species (e.g. in *Trichomonas vaginalis*).