Study of the antitypanosomal efficacy of the antidepressant drug sertraline

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Chagas disease (CD) is caused by the protozoan parasite Trypanosoma cruzi and affecting more than 8 million people worldwide. Existing antiparasitic drugs for Chagas disease have significant toxicity and suboptimal effectiveness. New therapeutic strategies are urgently needed to fight this neglected tropical disease. Using the drug repurposing approach, we evaluated the antiparasitic efficacy of the oral antidepressant sertraline (SER) using in vitro and in vivo models. Trypomastigotes were incubated with SER and the cell viability was determined by resazurin. After 24 h, 100% of the parasites were eliminated at the highest tested concentration, with an IC₅₀ value of 1.8 µM. Intracellular amastigotes (Y strain) in macrophages cells were also susceptible, demonstrating an IC₅₀ value of 1.46 µM. When incubated with intracellular amastigotes in cardiomyocytes (CM) cells, sertraline showed an IC₅₀ value of 6.6 µM. The mammalian cytotoxicity in L929 cells and cardiomyocytes was determined after 48 h incubation, and resulted in a 50% cytotoxic concentration (CC₅₀) of 11.5 µM and 25.0 µM, respectively. Sertraline efficacy was investigated in Swiss male mice infected with bloodstream parasites (Y strain); SER was administered twice a day at 10 mg/kg via intraperitoneal route (i.p) and 40 mg/Kg orally (p.o) for 5 consecutive days. Benznidazole was used at 100 mg/kg/day as the reference drug. When administered at 10 mg/kg i.p. SER showed low efficacy, reducing the parasitaemia by 20% at the onset. At 40 mg/Kg, sertraline showed no efficacy and increased the parasitaemia by 57% when compared the untreated group. At 10 mg/kg i.p., SER increased the survival rate of animals by 20%, with a gradual increase in body weight. Although SER showed low in vivo efficacy, the drug was potent against trypomastigotes and intracellular amastigotes and could be used as scaffold for the synthesis of new derivatives in drug design studies for Chagas disease.

Keywords: Chagas disease, drug repositioning, sertraline.

Supported: FAPESP 2015/23403-9 and CAPES.