Diazepam pode induzir proliferação tumoral. O clonazepam é mais seguro

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O diazepam induz a proliferação tumoral e o clonazepam não induz.


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The Translocator Protein (TSPO), previously known as the peripheral-type benzodiazepine receptor, is a ubiquitous drug- and cholesterol-binding protein that is up regulated in several types of cancer cells. TSPO drug ligands (e.g., diazepam) induce or inhibit tumor cell proliferation, depending on the dose and tissue origin. We have previously shown that TSPO is expressed in Ehrlich tumor cells and that diazepam increases proliferation of these cells in vitro. Here, we investigated the in vivo effects of diazepam on Ehrlich tumor growth and the role of TSPO in mediating this process. Oral administration of diazepam to mice (3.0mg/kg/day for 7 days) produced plasma and ascitic fluid drug concentrations of 83.83 and 54.12 nM, respectively. Diazepam increased Ehrlich tumor growth, likely due to its ability to increase tumor cell proliferation and Reactive Oxygen Species production. Radioligand binding assays and nucleotide sequencing revealed that Ehrlich tumor cell TSPO had the same pharmacological and biochemical properties as TSPO described in other tumor cells. The estimated K(d) for PK 11195 in Ehrlich tumor cells was 0.44 nM and 8.70 nM (low and high binding site, respectively). Structurally diverse TSPO drug ligands with exclusive affinity for TSPO (i.e., 4-chlordiazepam, Ro5-4864, and isoquinoline-carboxamide PK 11195) also increased Ehrlich tumor growth. However, clonazepam, a GABA(A)-specific ligand with no affinity for TSPO, failed to do so. Taken together, these data suggest that diazepam induces in vivo Ehrlich tumor growth in a TSPO-dependent manner.

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Effects of peripheral-type benzodiazepine receptor ligands on Ehrlich tumor cell proliferation.


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Peripheral-type benzodiazepine receptors have been found throughout the body, and particularly, in high numbers, in neoplastic tissues such as the ovary, liver, colon, breast, prostate and brain cancer. Peripheral-type benzodiazepine receptor expression has been associated with tumor malignity, and its subcellular localization is important to define its function in tumor cells. We investigated the presence of peripheral-type benzodiazepine receptors in Ehrlich tumor cells, and the in vitro effects of peripheral-type benzodiazepine receptors ligands on tumor cell proliferation. Our results demonstrate the presence of peripheral-type benzodiazepine receptor in the nucleus of Ehrlich tumor cells (85.53 +/- 12.60%). They also show that diazepam and Ro5-4864 (peripheral-type benzodiazepine receptor agonists) but not clonazepam (a molecule with low affinity for the peripheral-type benzodiazepine receptor) decreased the percentage of tumor cells in G0-G1 phases and increased that of cells in S-G2-M phases. The effects of those agonists were prevented by PK11195 (a peripheral-type benzodiazepine receptor antagonist) that did not produce effects by itself. Altogether, these data suggest that the presence of peripheral-type benzodiazepine receptor within the nucleus of Ehrlich tumor cells is associated with tumor malignity and proliferation capacity.

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