Calcium signaling

Mechanistically, Tumor-Treating Fields have been proposed to impair formation of the mitotic spindle apparatus and cytokinesis. In order to identify further potential molecular targets, here the effects of TTFields on Calcium signaling, ion channel activity in the plasma membrane, cell cycle, cell death, and clonogenic survival were tested in two human glioblastoma cell lines in vitro by fura-2 Ca2+ imaging, patch-clamp cell-attached recordings, flow cytometry and pre-plated colony formation assay. In addition, the expression of voltage-gated Ca2+ (Cav) channels was determined by real-time RT-PCR and their significance for the cellular TTFields response defined by knock-down and pharmacological blockade. As a result, TTFields stimulated in a cell line-dependent manner a Cav1.2-mediated Ca2+ entry, G_1 or S phase cell cycle arrest, breakdown of the inner mitochondrial membrane potential and DNA degradation, and/or decline of clonogenic survival suggesting a tumoricidal action of TTFields. Moreover, inhibition of Cav1.2 by benidipine aggravated in one glioblastoma line the TTFields effects suggesting that Cav1.2-triggered signaling contributes to cellular TTFields stress response. In conclusion, the present study identified Cav1.2 channels as TTFields target in the plasma membrane and provides the rationale to combine TTFields therapy with Ca2+ antagonists that are already in clinical use [1)].

1)
Neuhaus E, Zirjacks L, Ganser K, Klumpp L, Schüler U, Zips D, Eckert F, Huber SM. Alternating Electric Fields (TTFields) Activate Ca(v)1.2 Channels in Human Glioblastoma Cells. Cancers (Basel). 2019 Jan 18;11(1). pii: E110. doi: 10.3390/cancers11010110. PubMed PMID: 30669316; PubMed Central PMCID: PMC6356873.