Investigation of the availability of sigma-1 receptors in orthotopic human glioblastoma-bearing mice with positron emission tomography (PET) using (*S*)-(−)-[^{18}F]fluspidine

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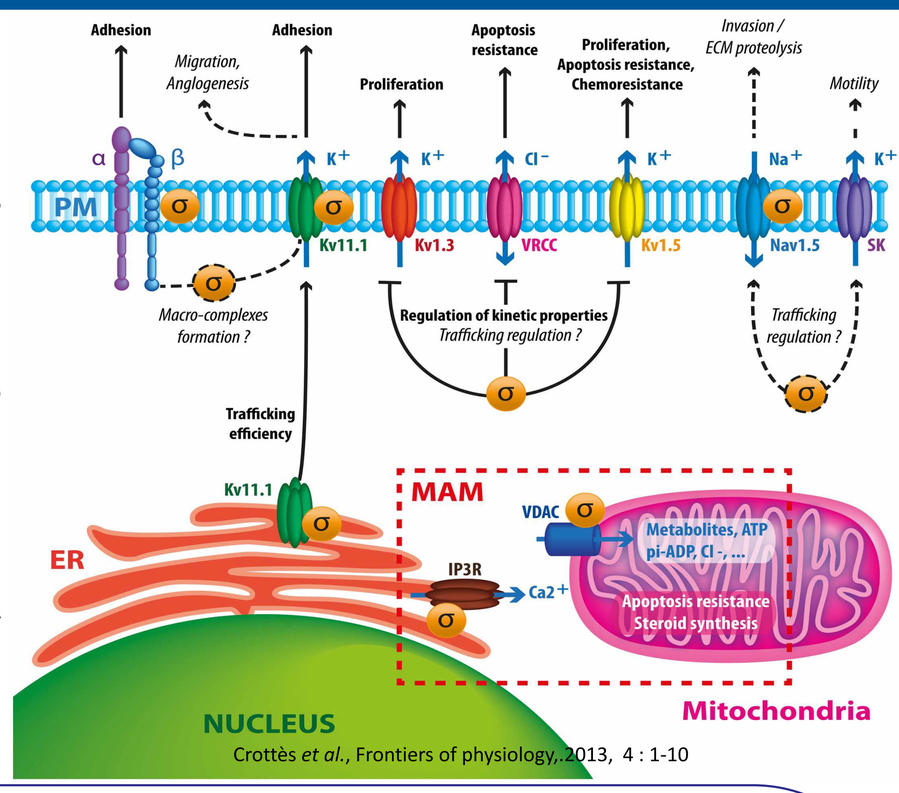
INTRODUCTION

The sigma-1 receptor (S1R) is a chaperone protein of the mitochondrion-associated endoplasmic reticulum membrane (MAM). Its expression is dysregulated in various cancers including glioblastoma, and ligand binding may decrease the proliferation of human glioblastoma cell lines. Thus, S1R characterization in glioblastoma could help to better understand the pathophysiology of this cancer and to improve diagnosis or treatment follow-up.

OBJECTIVES

We aim to evaluate the potential of (*S*)-(−)-[^{18}F]fluspidine, a highly specific S1R radioligand already applied in clinical studies, to characterize S1R expression in an orthotopic glioblastoma model in mouse with small-animal PET/MRI.

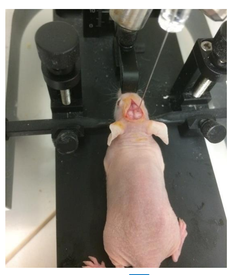


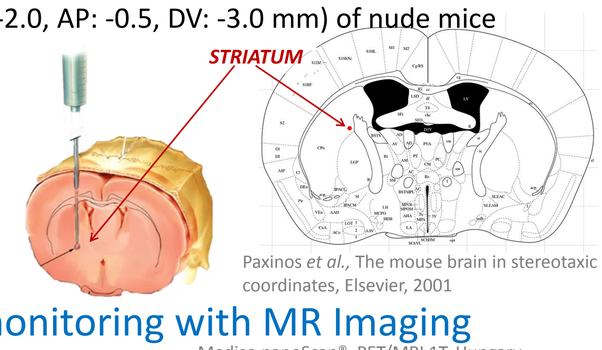
Crottès *et al.*, Frontiers of physiology,.2013, 4 : 1-10

Animal model

Stereotactic injection of U87 cells

- human glioblastoma, 50 000 cells/1µl
- in the *striatum* (L: -2.0, AP: -0.5, DV: -3.0 mm) of nude mice

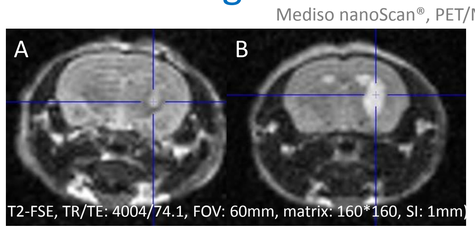




Paxinos *et al.*, The mouse brain in stereotaxic coordinates, Elsevier, 2001

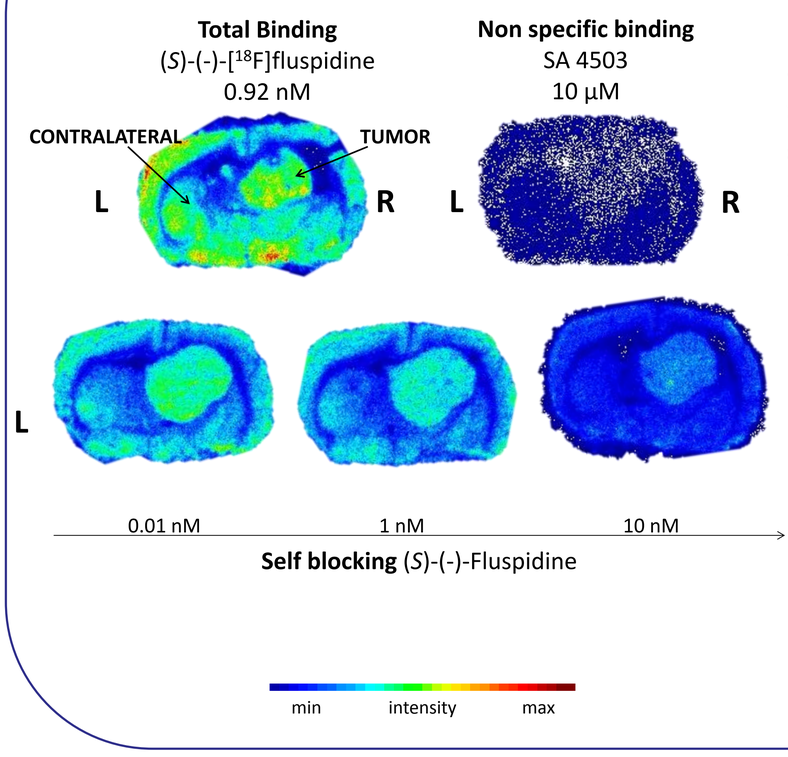
Tumor monitoring with MR Imaging

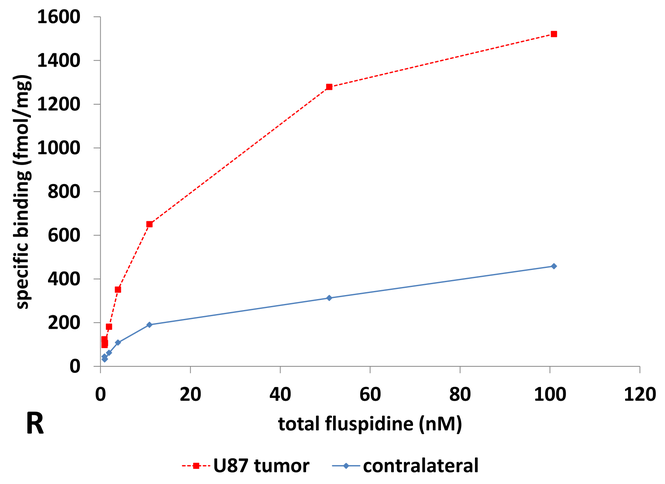
Mediso nanoScan®, PET/MRI 1T, Hungary



T2 weighted images of a nude mouse brain showing the growth of a U87 tumor **A**) 7 days post-injection and **B**) 16 days post-injection in the coronal plan

In vitro autoradiography

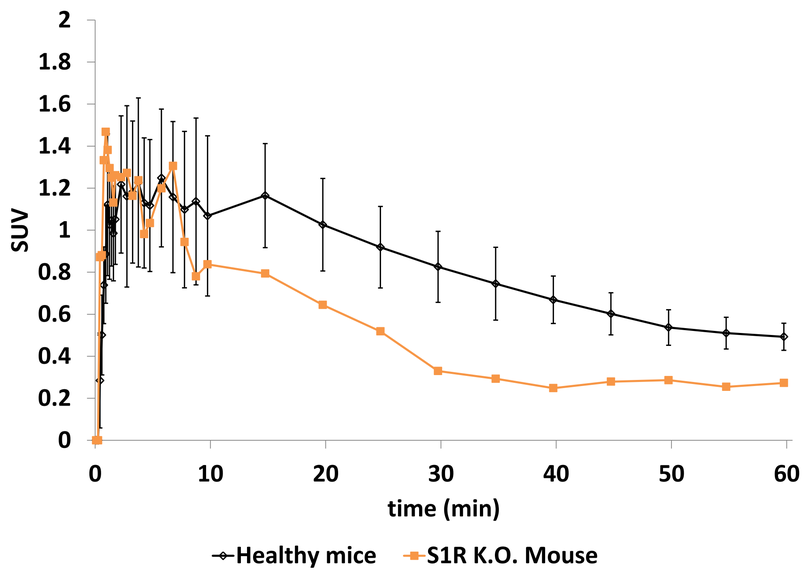




	tumor	contralateral side
B_{max} (fmol/mg)	1756±40	490±43
K_D (nM)	17.5±1.3	17.0±4.8
relative density	3.6	1.0

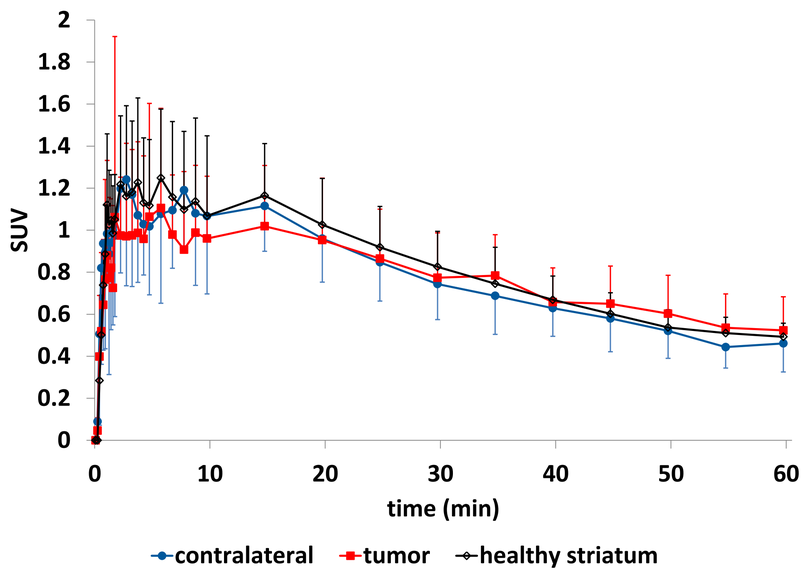
PET imaging of (*S*)-(-)-[^{18}F]fluspidine

in healthy mice and **S1R K.O.** mouse



In vivo validation of the specific binding for S1R shown by the higher SUV values obtained in *striatum* of healthy mice (n=3) compared to the S1R K.O. mouse (n=1)

in mice bearing **U87 orthotopic tumor**

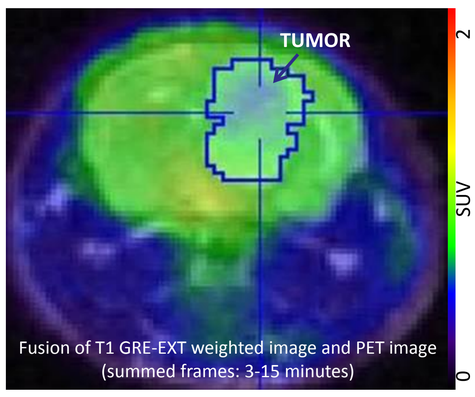


Time-activity curves of the striatum of healthy mice (n=3), of the tumor region (n=17, average volume: 12 mm³) and the contralateral side(n=17) of tumor mice. The PET image shows spatial uptake inhomogeneities in the tumor

Peak-to-end ratio

	mean	SD
tumor	1.65* (p=0.001)	0.46
contralateral	2.19	0.59
healthy striatum	2.11	0.38

Two-tailed paired student T-test, p<0.05. *compared to CL



SUMMARY

- The *in vitro* autoradiography revealed a higher S1R density in the tumor compared to the contralateral side.
- The PET investigation revealed a significant difference in the pharmacokinetics of (*S*)-(-)-[^{18}F]fluspidine between tumor and contralateral region, probably related to different S1R availabilities.
- These first results show the suitability of (*S*)-(-)-[^{18}F]fluspidine for characterization of U87 S1R status.

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