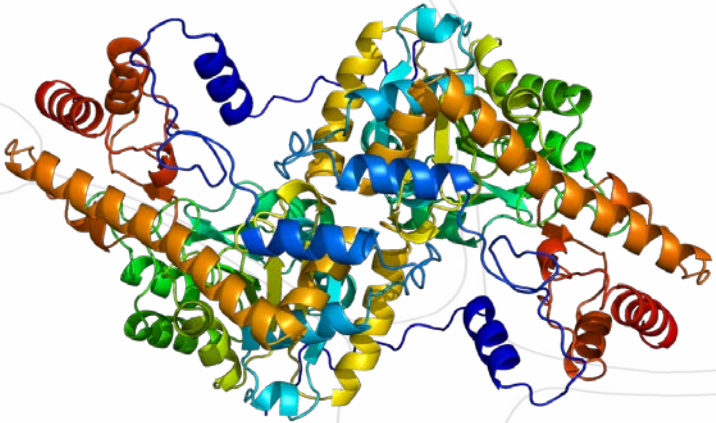
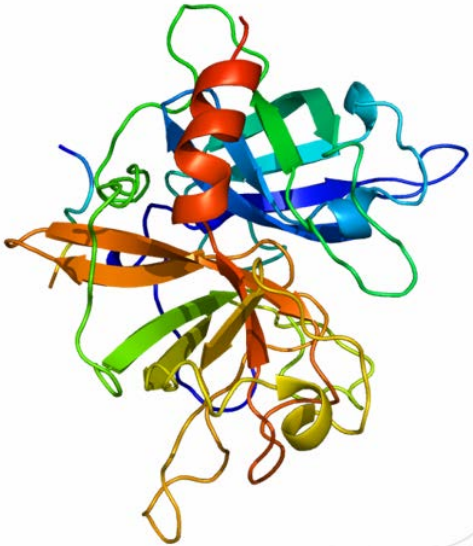
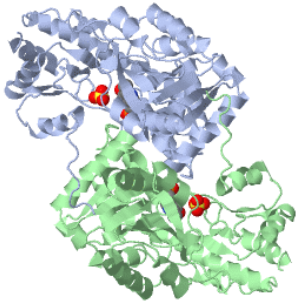
Estudio de interacción entre GOT y tPA para una futura aplicación clínica



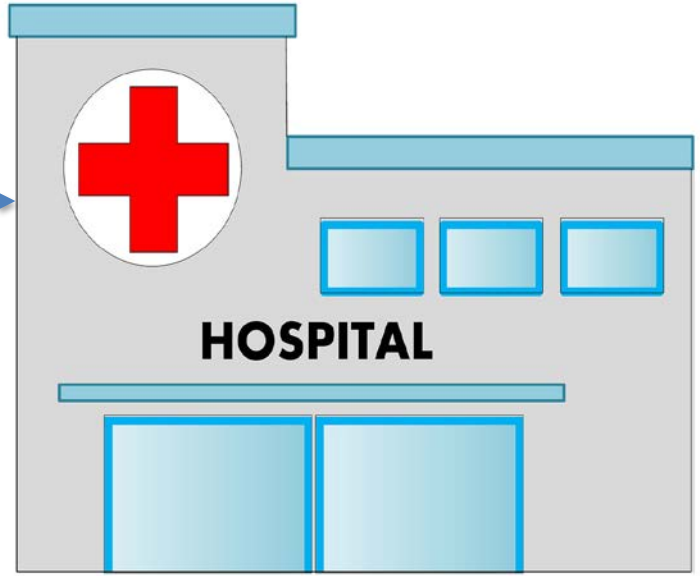


Introducción



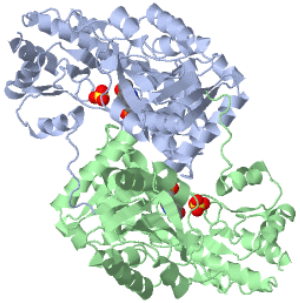
rhGOT

(fase aguda; <5h)



GOTIS ***(GOT for ischemic stroke)***

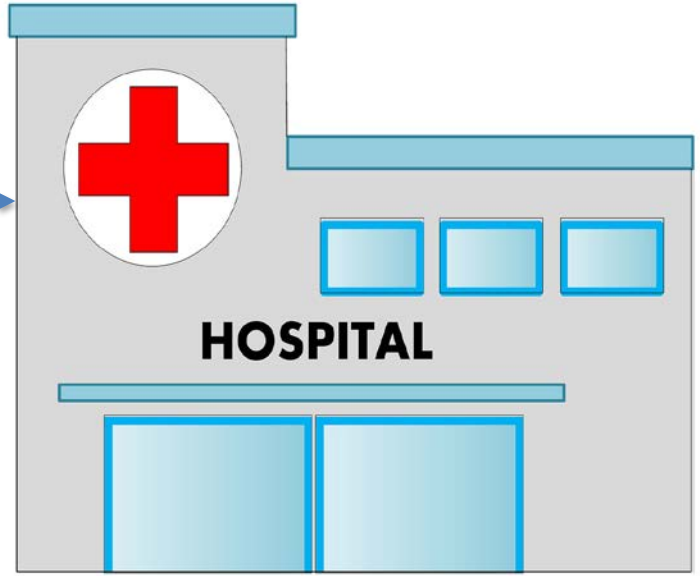
Introducción



rhGOT

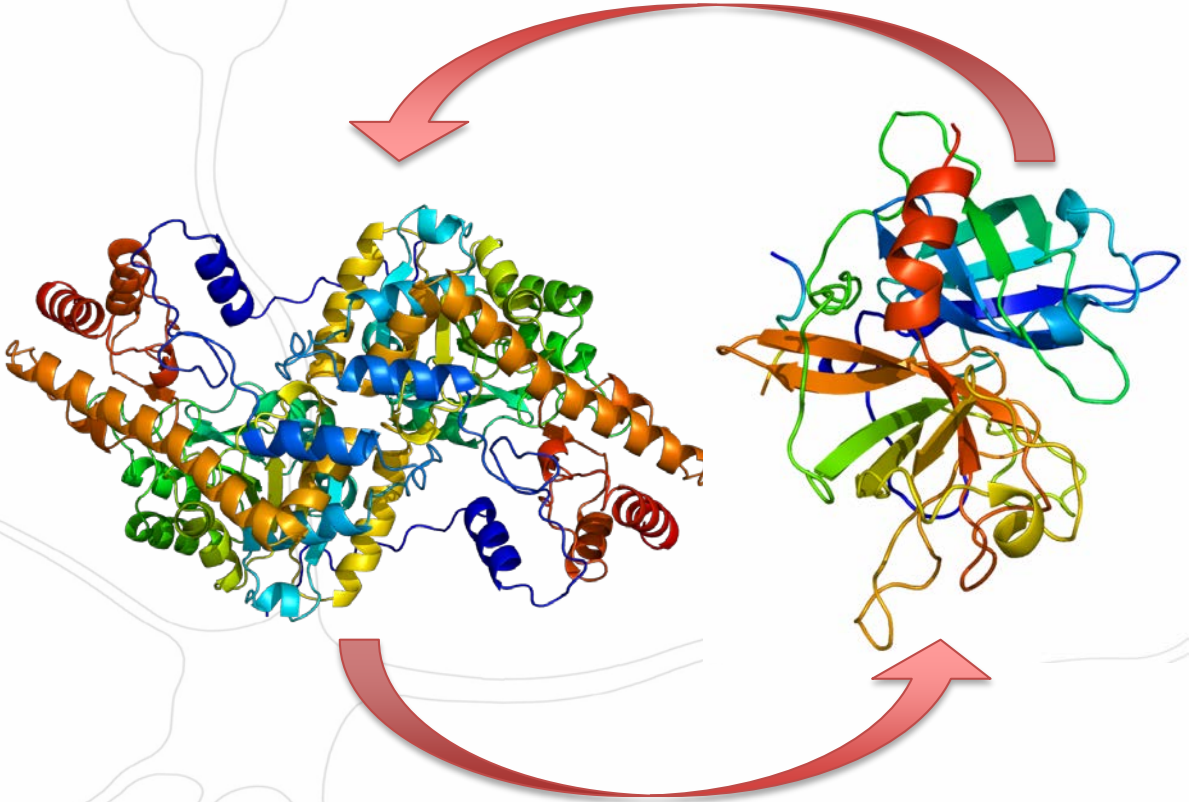
(fase aguda; <5h)

(rtPA; <4,5h)



GOTIS ***(GOT for ischemic stroke)***

Introducción



Introducción

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

STROKE

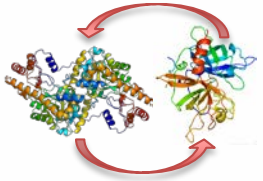
Plasmin-resistant PSD-95 inhibitors resolve effect-modifying drug-drug interactions between alteplase and nerinetide in acute stroke

Diana Mayor-Nunez[1,2,3], Zhanxin Ji[1], Xiujun Sun[1], Lucy Teves[3], J. David Garman[1], Michael Tymianski[1,2,3,4]*

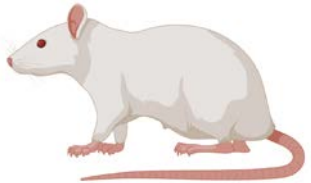
Neuroprotection for acute ischemic stroke is achievable with the eicosapeptide nerinetide, an inhibitor of the protein-protein interactions of the synaptic scaffolding protein PSD-95. However, nerinetide is subject to proteolytic cleavage if administered after alteplase, a standard-of-care thrombolytic agent that nullifies nerinetide's beneficial effects. Here, we showed, on the basis of pharmacokinetic data consistent between rats, primates, and humans, that in a rat model of embolic middle cerebral artery occlusion (eMCAO), nerinetide maintained its effectiveness when administered before alteplase. Because of its short plasma half-life, it can be followed by alteplase within minutes without reducing its neuroprotective effectiveness. In addition, the problem of protease sensitivity is solved by substituting cleavage-prone amino acids from their L- to their D-enantiomeric form. Treatment of rats subjected to eMCAO with such an agent, termed D-Tat-L-2B9c, eliminated protease sensitivity and maintained neuroprotective effectiveness. Our data suggest that both the clinical-stage PSD-95 inhibitor nerinetide and protease-resistant agents such as D-Tat-L-2B9c may be practically integrated into existing stroke care workflows and standards of care.

Bloques experimentales

- Interacción de GOT y rtPA *in vitro*

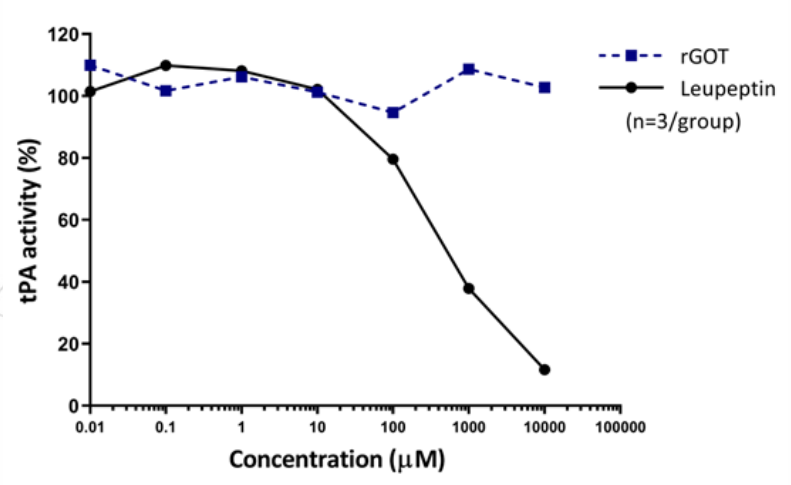


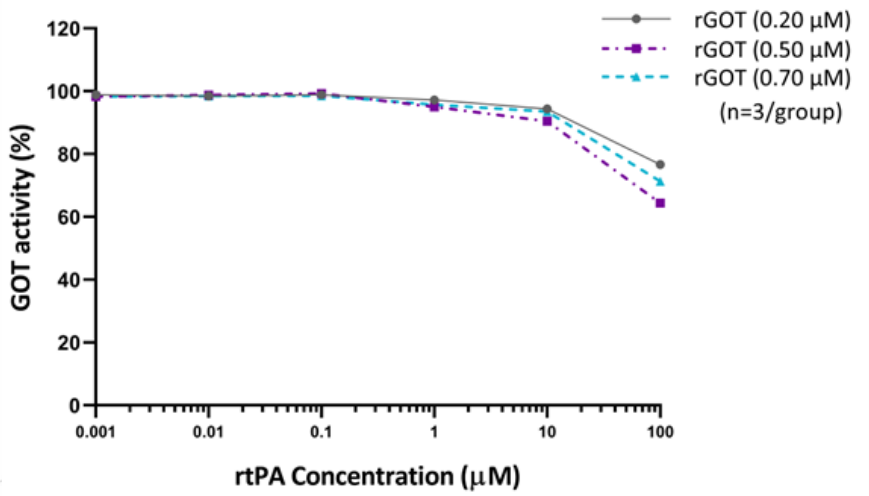
- Interacción de GOT y rtPA en la respuesta *in vivo* en ratas sanas



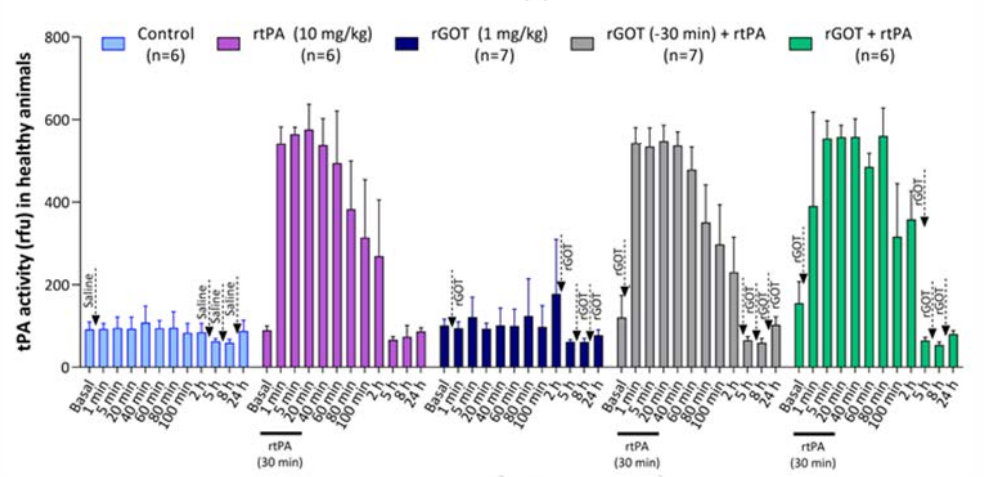
- Interacción de GOT y rtPA en la respuesta *in vivo* en MCAO

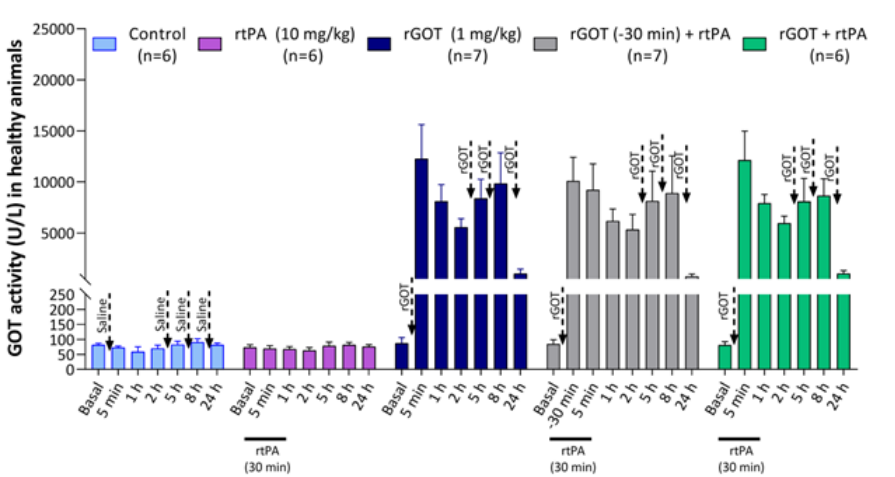
Resultados *in vitro*



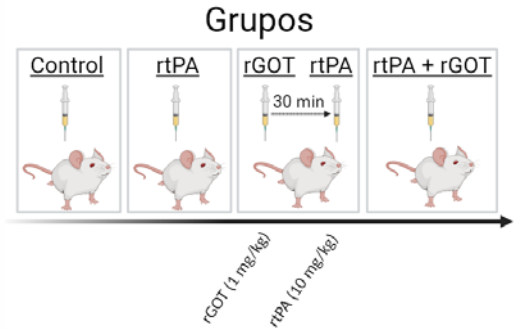


Respuesta *in vivo* en animales sanos

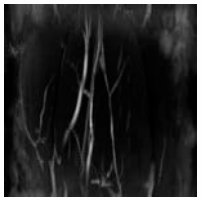


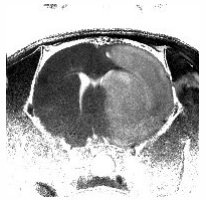


Protocolo de respuesta en MCAO



tPA (10 mg/kg) o salino

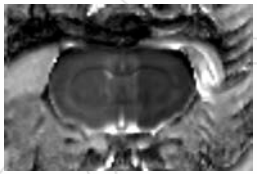


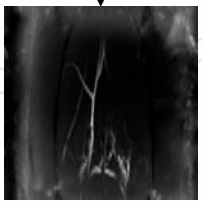


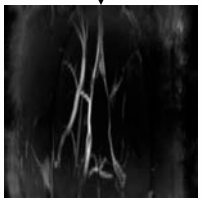
Extracción de sangre → Cirugía → Oclusión 30 min → Angiografía y DWI 30 min → Inyección tratamiento 30 min → Angiografía y DWI → Angiografía y T2 24h

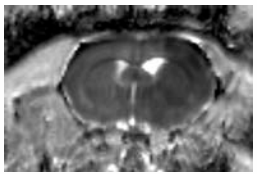
rGOT (1 mg/kg) o salino

rGOT (1 mg/kg) o salino





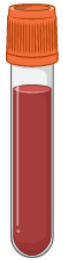


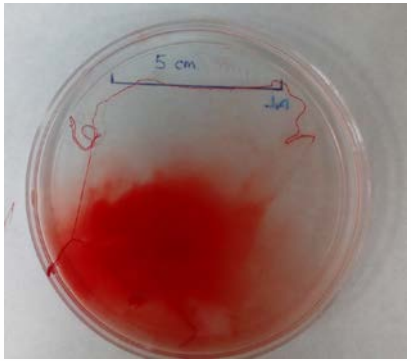


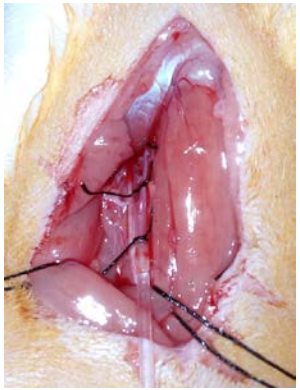
Oclusión

Registro Doppler

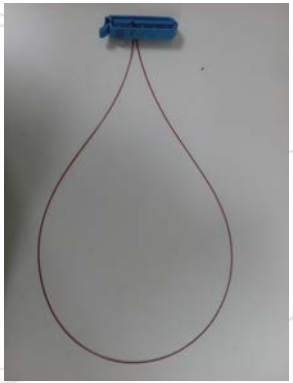
Protocolo eMCAO

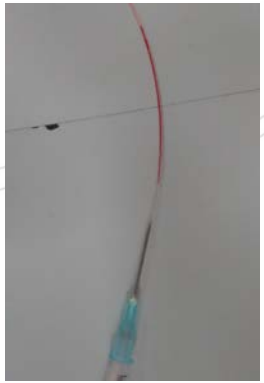




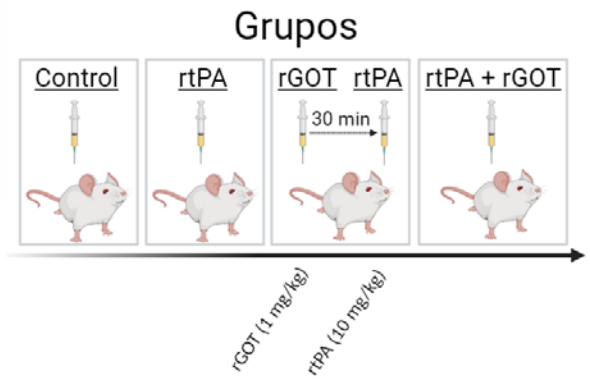


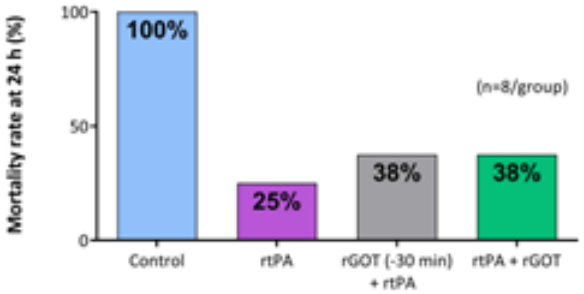
Extracción de sangre → Introducción en un tubo → Incubación → Extracción y cortado → Introducción en otro tubo → Canulación → Inyección del trombo

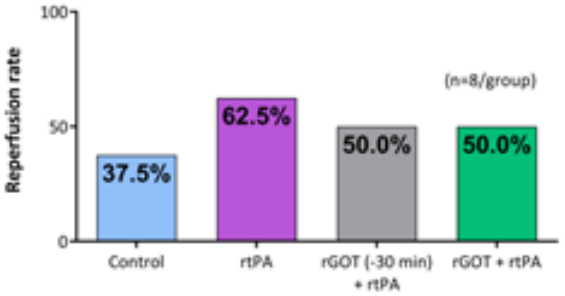


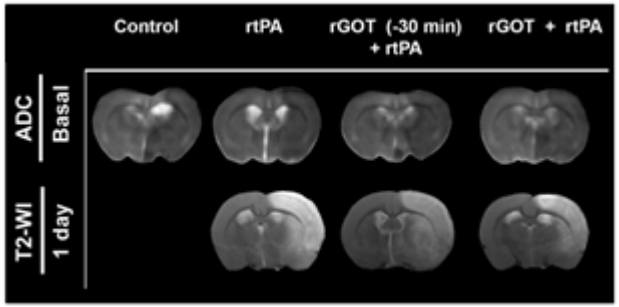


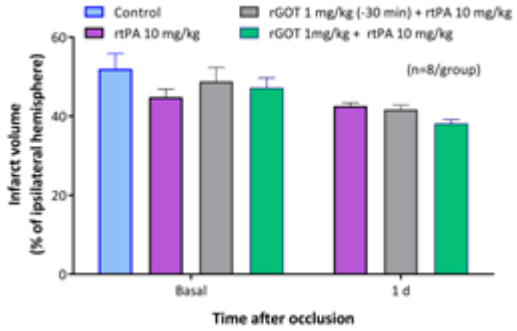
Resultados de respuesta en MCAO











Conclusión

El análisis de interacción entre rGOT y rtPA demostró que ambas enzimas pueden combinarse simultáneamente sin interferir con las actividades de la otra. Estos resultados también muestran que la terapia con rGOT puede iniciarse incluso en una fase muy temprana después del inicio de la isquemia (antes de la terapia de reperfusión) para ralentizar la expansión de la lesión isquémica y potencialmente aumentar la ventana temporal y el número de pacientes tratados con éxito con trombólisis o trombectomía mecánica.