

Letter to the editor

The CXCR7 activation by SDF1 induces Neural progenitor migration (NPC): a dual effect on CXCR4/CXCR7 axis within the vascular niche of ischemic rats

Dear Editor, there is a certain controversy about the protective role of SDF1 Alpha in the pathophysiology of cerebral ischemia and its interaction with CXCR4 and CXCR7 Alpha chemokine receptors. Can SDF1 Alpha induce neuroprotective or neurotoxic events in the vascular niche of ischemia rats?

Huang *et al.* 2012 recently published that AMD3100, a CXCR4 antagonist, reduced cytokine release in the ischemic cortex as well as induced blood-brain barrier dysfunction after middle cerebral artery occlusion when the drug was administered at a dose of 1 mg/kg for three-days after ischemia, i.p (1). However, their study did not consider whether SDF1 Alpha = CXCL12 could activate CXCR7 chemokine receptor as CXCL12 has 10 times affinity for CXCR7 than it does for CXCR4 but does not signal through G coupled proteins, in contraposition to CXCR4. Thus, part of the AMD3100 protective effects produced by AMD3100 that reported Huang *et al.* 2013 could be due to CXCR7 activation since is an inverse agonist for CXCR7 (2). Another recent study published in Plos One by Ramos Cejudo *et al.*, 2012 described a reduced mRNA CXCR4 expression after ischemia in the perinfarct area, as compared with the core (3). These findings are in contraposition with the

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'reparative' role report by CXCR4/SDF1 Alpha within the vascular niche (2).

The study by Ramos Cejudo *et al.*, 2012 detecting CXCR4 downregulation argued that chemokines induce stem cell trafficking (3). CXCR4/SDF1 Alpha are cue factors that promote neurogenesis and angiogenesis within the vascular niche in cerebral ischemia (4). In addition, AMD3100 reduces MPO activity in AMD3100-treated ischemic rats (1). However, we must not underconsider the role of CXCR7 activation by SDF1 Alpha = CXCR7 because this ligand induces NPC migration within the periinfarct area because AMD3100 can also act as an inverse agonist for CXCR7 (2). Moreover, CXCR7 signaling attenuates the adaptative cellular response to acute SDF1 Alpha stimulation (≤ 12 h) after hypoxia (5). Thus, part of the protective effects reported by Huang could be attributed to AMD3100 acting as an inverse agonist for CXCR7 (2). Interestingly, CXCL12 increases human neural progenitor cell survival through a CXCR7- and CXCR4-mediated endocytotic mechanism (6).

In addition, can microarrays for the CXCR4/SDF1 Alpha axis really detect functional chemokine receptor activation within the periinfarct area in the Ramos Cejudo's study? CXCR4/CXCR7/SDF1 Alpha can be located on neurons and glial cells. Thus, the Ramos Cejudo *et al.*, 2012 study report that CXCR4 downregulation does not distinguish between neuronal or glial CXCR4 expression. In addition, CXCR4/CXCR7 undergoes posttranslational modifications (ubiquitination or dimerization), which cannot be detected by microarrays. Moreover, their study does not address the question of whether CXCR4 changes might be regulated differentially by either neurons or glial cells. We think that the reported CXCR4 downregulation is no more than a conse-

quence of compensatory CXCR4 changes between neuronal and glial responses as microarrays cannot distinguish between the percentages that belong to either cell type in the Ramos-Cejudo study. This distinction is crucial for understanding the neurotoxic cascade within the vascular niche in cerebral ischemia. In our opinion, these two aspects must be studied and differentiated in the perinfarct area because CXCR7 activation promotes antiapoptotic and proliferation effects in NPC.

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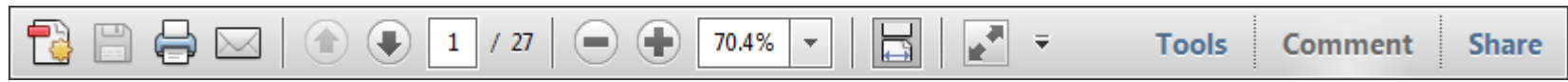
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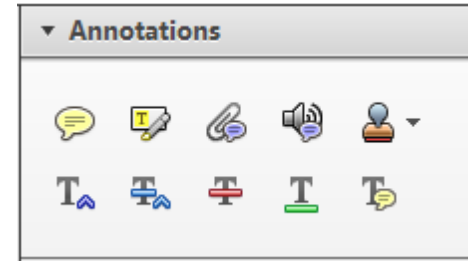
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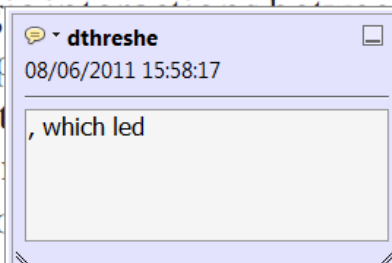


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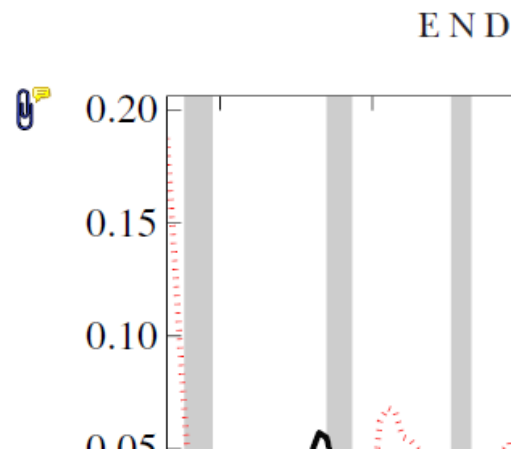
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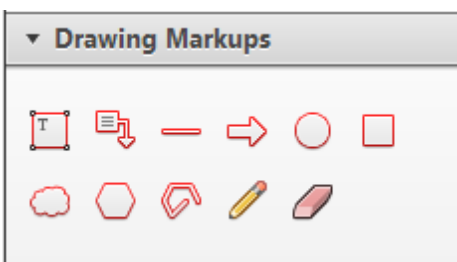


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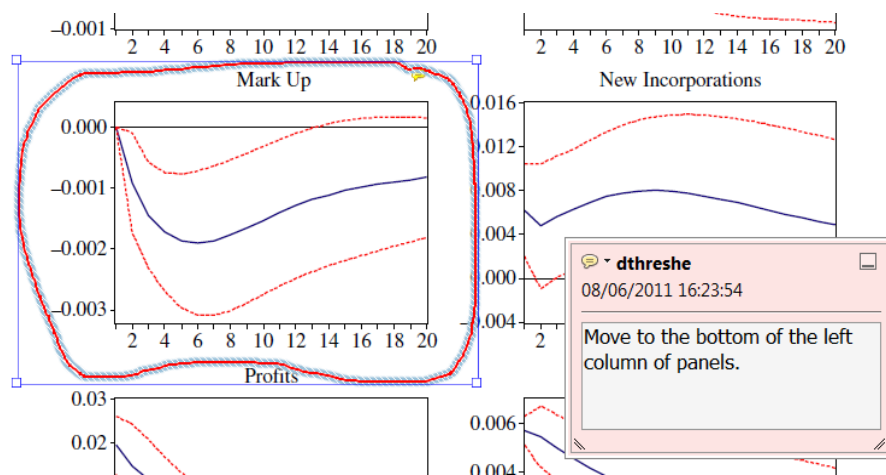


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