



Unfolding the cardioprotective potential of sigma-1 receptor-directed molecular imaging

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As a chaperone crucially involved in protein folding,¹ Sigma-1 receptor (Sig-1R) has been extensively investigated in the context of neurodegenerative disorders, such as Parkinson's or Alzheimer Disease.^{1–3} In recent years, it has also gained interest within the cardiovascular community, as it exerts cardioprotective effects against a.) apoptosis, b.) hypertrophy and c.) maladjusted endoplasmic reticulum stress response.¹ In this regard, a Sig-1R *in-vivo* molecular imaging approach may not only provide further insights into cardiac ischemia post-myocardial infarction,⁴ but also in the context of hypertrophy-related vascular injury.^{1,5} In the present study, Wakabayashi and coworkers focused on myocardial ischemic burden and the targeting of Sig-1R using the SPECT probe I-125-iodophenyl-piperidino-cyclopentanol (125I-OI5V).⁶ Left coronary occlusion (LCA) was conducted over varying time frames of 10 to 30 min, followed by release of the snare, thereby allowing for reperfusion. 125I-OI5V increased depending on the ischemia time. Second, triple-radiotracer autoradiography including the myocardial perfusion probes 99mTc-MIBI and 201TI revealed that 125I-OI5V uptake ratio was negatively associated with 201TI

uptake ratio, supporting the notion that the observed 125I-OI5V accumulation in areas of risk is not only related to the time of LCA, but also depending on reduced 201TI uptake. As such, SIG-1R expression may provide a read-out of the severity of ischemic burden. In addition, 125I-OI5V uptake was also mainly located in and adjacent to (CD68-positive) areas of macrophage infiltration.⁶ Although the herein used triple-tracer autoradiography approach is challenging and crucial for understanding the underlying uptake mechanism, the authors may have also provided further evidence on the feasibility of *in-vivo* imaging, as they have previously demonstrated in an ischemia–reperfusion model limited to 30 min using the identical radiotracer.⁴ Second, the most recent work of Wakabayashi et al. published in this journal would have benefit from a more relevant clinical scenario.⁶ For instance, in transient coronary occlusion models in rats, treatment with the selective Sig-1R agonist, 2-(4-morpholinoethyl)-1-phenylcyclohexane-1-carboxylate hydrochloride (PRE-084) led to improvement in cardiac outcome parameters, such as ejection fraction.⁷ As such, future studies may also consider an image-guided treatment approach.⁸ In this regard, rats could be treated with this Sig-1R antagonist at the time of maximum of target expression as provided by *in-vivo* 125I-OI5V SPECT and compared to off-peak treated animals, as it has been recently demonstrated for C-X-C motif chemokine receptor-targeted molecular imaging in murine studies.⁹ Such an image-guided treatment would then link the herein observed 125I-OI5V uptake in damaged myocardium to a clinical meaning, in particular as the identical target would be used for both imaging and therapy. Such an assessment of the retention capacities prior to treatment on-set using Sig-1R antagonist would then resemble the widely adopted

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theranostic concept in nuclear oncology.^{10,11} Nonetheless, the present work by Wakabayashi et al. is of importance,⁶ as it provides the first step towards such an outcome-oriented experimental set-up.

Beyond its use for ischemic burden, other cardiovascular applications would be of even greater interest. As alluded to earlier, the role of Sig-1R in the context of hypertrophy has been already investigated.⁵ In this regard, the vasculo-protective effect of Sig-1R on pressure overload hypertrophy-induced damage in the thoracic aorta has been already demonstrated by using Wistar rats,⁵ i.e., the identical species that had also been used by Wakabayashi et al. in the present study.⁶ In a sophisticated animal model of vascular injury caused by pressure overload, the Sig-1R agonist flvoxamine led to restored pressure and protected against hypertrophy via upregulation of Sig-1R and stimulation of Sig-1R mediated Akt phosphorylation and endothelial nitric oxide synthase signaling.⁵ Again, using 125I-OI5V in the context of pressure overload and hypertrophy, the Sig-1R retention capacities could be quantified, which may then allow to improve outcome in pressure overload-related vascular damage by initiating flvoxamine treatment at the maximum of the SPECT signal. This would be even become more relevant if other Sig-1R-directed antihypertensive drugs would be developed.¹ For instance, mice scheduled for transverse aortic constriction (TAC) could then be used and improvement of contractile function could then be investigated in animals treated at the maximum of 125I-OI5V uptake. Of note, such TAC models have just been recently successfully investigated using the most commonly used PET radiotracer 18F-FDG.¹²

Taken together, with its chaperone activity involved in protein folding, a direct *in-vivo* visualization of Sig-1R may be of interest in various clinical scenarios, in particular if Sig-1R drugs providing cardioprotective effects would become available. Until that, the beneficial impact of Sig-1R-targeted molecular imaging in the context of cardiovascular care may remain rather unfolded.

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Disclosures

The authors declare that they have no conflict of interest.

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