

Title

Kinetic modelling and test-retest reproducibility of the selective PET radiotracer [¹⁸F]2FNQ1P for serotonin 5-HT₆receptor imaging in pigs

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Aim

[¹⁸F]2FNQ1P is a new PET radiotracer with highly specific and selective binding to 5-HT₆ receptors (1,2). Preclinical studies, especially in non-human primates, suggest that [¹⁸F]2FNQ1P is a reliable PET radiotracer for visualization and quantification of 5-HT₆ receptors in the brain (3).

The objectives of this study were to perform a full PET kinetic modeling of [¹⁸F]2FNQ1P using arterial input function (AIF) in pigs, to identify a reference region suitable for a simplified modeling method, and to assess reproducibility with test-retest scans.

Materials and Methods

8 male or female pigs (33.6 ± 2.0 kg) underwent MRI scans and two 90-min [¹⁸F]2FNQ1P PET/CT scans in a test-retest protocol, with arterial input function (AIF) in the second session. Regional time-activity curves (TAC) were obtained by co-registering the MRI and PET images to Saikali's pig atlas (4).

Kinetic models were compared (one-tissue compartment and two-tissue compartment) and two reference region models were evaluated (simplified reference tissue model, SRTM, and the Logan reference model, LREF). For each model, two different reference regions were assessed : vermis and corpus callosum (CC).

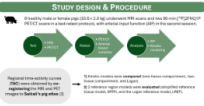


Fig. 1: Study design & procedure

Results

The mean plasma-to-whole blood ratio was 0.98±0.11, suggesting an equal distribution between plasma and blood. The free plasma fraction remained stable over time with a mean value of 17.4±1.6%. The radiotracer was metabolized and progressively decreased from 59.9±23.4% (1-min post-injection) to 25.9±17.4% of the parent fraction (90-min post-injection) (Figure 2). TAC showed facilitated intracerebral crossing (Figure 2). Interestingly, cerebellum, vermis and insula showed rapid and high uptake followed by a notable fast washout phase. At the end of acquisition (90-min), striatum, amygdala and frontal cortex presented the highest steady-state value while cerebellum and vermis showed the lowest. Vermis and corpus callosum appeared as a possible reference region for simplified kinetic modeling. Figure 4 shows a PET overlay on MRI, demonstrating sufficient signal intensity and contrast for voxel-wise parametric imaging. Interestingly, an important signal was detected in a region identified as the pituitary gland (not included in the atlas). Furthermore, the voxels clusters with highest uptake were located in the caudate nucleus, putamen, prefrontal cortex, and frontal cortex.

Concerning modeling studies, the Akaike Information Criterion (AIC) showed a slight advantage for a one-compartment model (438.83±19.82) over a two-compartment model (446.78±24.20). Reference region modeling was performed using the vermis and corpus callosum. Detailed results are presented in Table 1. The best model appeared to be obtained with LREF, as regression coefficients were 0.89±0.13 for LREF_{CC} and 0.93±0.07 for LREF_{vermis}, while they were 0.34±0.26 for DVR_{SRTM} and 0.54±0.25 for SRTM_{vermis}. Regarding test-retest parameters, DVR values were more highly correlated with LREF, with equivalent values for CC (R²=0.74±0.14) or Vermis (R²=0.74±0.15). The best reliability was found for the LREF method with the vermis as a reference region (Bias = -4.33%). Results are presented in Table 2.

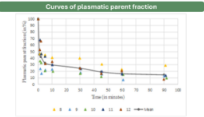


Fig. 2: Curves of parent fraction. Triangles (▲) numbered from 8 to 12 represent data from pigs used to generate our model. The curve labeled 'Mean' (—) represents the mean curve generated from the averages of the other 5 previous pigs.

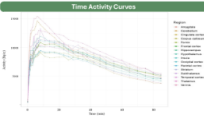


Fig. 3: Illustration of TACs (Time-Activity Curves) in various cerebral areas reveals that the cerebellum, vermis, and insula exhibit rapid decreases, suggesting their potential utility as reference regions.

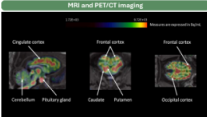


Fig. 4: Facilitated intracerebral crossing was observed without the need for discloripine or tariquidar, leading to contrast in easily identifiable regions of the brain. The scan showed high uptake in the pituitary gland, striatum (caudate and putamen), and frontal and occipital cortex, indicating significant activity in these regions.

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Mean regression parameters over DVR _{LREF}				Mean test-retest parameters			
	Regions	Slope	Intercept	R ²	ICC	Bias	Var (%)
DVR _{CC}	CC	0.88±0.20	0.09±0.23	0.74±0.14	0.50±0.34	-4.78	16.30
	Vermis	0.88±0.11	0.10±.18	0.74±0.15	0.55±0.18	-4.33	18.87
DVR _{vermis}	CC	0.17±0.21	0.74±0.16	0.66±0.07	0.15±0.41	5.06	83.66
	Vermis	0.49±0.13	0.53±0.11	0.25±0.10	0.19±0.35	-7.28	26.16

Mean test-retest parameters			
ICC	Bias	Var (%)	
0.50±0.34	-4.78	16.30	
0.55±0.18	-4.33	18.87	
0.15±0.41	5.06	83.66	
0.19±0.35	-7.28	26.16	

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Model		Reference region	Mean regression parameter compared to DVR _{LREF}			Mean regression parameter compared to DVR _{RREF}		
			Slope	Intercept	R ²	Slope	Intercept	R ²
DVR _{LREF}	CC		0.91±0.10	0.64±0.06	0.89±0.13	0.90±0.11	0.65±0.08	0.88±0.15
	Vermis		1.06±0.07	-0.02±0.04	0.93±0.07	1.05±0.07	-0.01±0.06	0.92±0.09
DVR _{RREF}	CC		0.47±0.33	0.57±0.35	0.34±0.26	0.49±0.34	0.57±0.34	0.34±0.25
	Vermis		0.62±0.25	0.36±0.24	0.54±0.25	0.63±0.25	0.35±0.25	0.56±0.26

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Mean regression parameter compared to DVR _{LREF}				
Model	Reference region	Slope	Intercept	
DVR _{CC}	CC	0.91±0.10	0.64±0.06	0.89±0.13
	Vermis	1.06±0.07	-0.02±0.04	0.93±0.07
DVR _{vermis}	CC	0.47±0.33	0.57±0.35	0.34±0.26
	Vermis	0.62±0.25	0.36±0.24	0.54±0.25

Tab. 1:

Conclusion

[¹⁸F]2FNQ1P has emerged as a reliable radiotracer for PET imaging to explore 5-HT₆ receptors in the brain. Its favorable brain uptake and pharmacokinetic profile open new perspectives for studying 5-HT₆ receptors.

Kinetic modeling using a one-compartment model with reference region approach provided reliable and reproducible results. The vermis and corpus callosum emerged as suitable reference regions, with the LREF method using the vermis demonstrating the best test-retest reliability.

Future studies are warranted to further explore the clinical implications of this approach.



Fig. 5: This work was partly funded by FLI and AIAIPLH

FLI = France Life Imaging and AIAIPLH = Association des Internes et Anciens Internes en Pharmacie des Hôpitaux de Lyon (Association of Residents and Former Residents in Hospital Pharmacy of Lyon)