COMMENTARY

[¹¹C]befloxatone distribution is well correlated to monoamine oxidase A protein levels in the human brain

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[¹¹C]befloxatone is a positron emission tomography radioligand to image monoamine oxidase A (MAO-A) in the brain, which has been used in preclinical studies and in clinical protocols. However, a recent study found that [¹¹C]befloxatone binding potential (k_3/k_4) has a poor correlation with MAO-A protein levels measured in the human brain. We here show that this poor correlation only depends on the choice of the parameter when performing kinetic modeling. In particular, the total volume of distribution of [¹¹C]befloxatone shows a tight correlation with both protein and mRNA levels of MAO-A in the human brain.

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In a recent work, Tong *et al.* reported the *in vitro* region-wise distribution of protein levels of monoamine oxidase A (MAO-A) in the human brain.¹ These results have important implications for brain imaging studies. Using data from published positron emission tomography (PET) studies, they found good correlations between *in vitro* MAO-A levels and PET measures of MAO-A density/activity using [¹¹C]harmine ($r=0.86$, $P=0.003$) and [¹¹C]clorgyline ($r=0.82$, $P=0.007$), but not with [¹¹C]befloxatone ($r=0.61$, $P=0.15$), essentially because of the low [¹¹C]befloxatone binding potential reported in the thalamus.² Thus, the authors suggested caution in interpretation of the data obtained with this radioligand. Two hypotheses can be put forward to explain this poor correlation: (1) the *in vivo* kinetics of [¹¹C]befloxatone poorly reflect the actual MAO-A distribution, and therefore [¹¹C]befloxatone should be abandoned; (2) the selected quantitative parameter, k_3/k_4 , is not the optimal one, and thus a different outcome parameter should be chosen.

The full kinetic modeling of [¹¹C]befloxatone has been recently published.³ This study showed that a two-tissue compartment model can reliably quantify total distribution volume (V_T) values. In agreement with *in vitro* data, the lowest [¹¹C]befloxatone V_T values were found in the cerebellum (6.7 ± 0.9 ml/cm³), while the highest were in the thalamus (19.3 ± 1.4 ml/cm³).³ Importantly, [¹¹C]befloxatone V_T values are well correlated with the *in vitro* MAO-A protein levels published by Tong *et al.*,¹ to a degree similar to that found for the other MAO-A radioligands ($r=0.78$, $P=0.008$) (Figure 1). Notably, the thalamus/cerebellum V_T ratio is slightly higher for [¹¹C]befloxatone (2.9), than for [¹¹C]harmine V_S (2.1) and [¹¹C]clorgyline λk_3 (2.4), thus indicating a slightly better, although still imperfect, quantitative proportionality with *in vitro* data (3.9).¹ Furthermore, [¹¹C]befloxatone compartmental V_T values are well correlated not only with protein levels, but also with mRNA expression of MAO-A,⁴ which suggests that MAO-A undergo little *in vivo* post-transcriptional modifications.

One possible reason why k_3/k_4 showed a poor correlation with protein levels might be due to the very slow wash-out from the brain of [¹¹C]befloxatone,³ which may introduce errors in the estimation of microparameters, especially k_4 . In addition, a K_1/k_2

Figure 1. Correlation between [¹¹C]befloxatone V_T values and *in vitro* MAO-A protein levels. Please compare this figure to Figure 6 in the paper by Tong and colleagues¹.

constrained model presupposes a constant non-displaceable compartment across the brain. If this condition is not verified, a regional quantification error may ensue.

Finally, in our kinetic modeling paper, we also showed that spectral analysis provided the most reliable quantification of [¹¹C]befloxatone at the voxel level.³ However, the correlation between protein levels and voxel-wise spectral analysis V_T values is weaker than with compartmental modeling ($r=0.67$, $P=0.033$). Therefore, compartmental modeling at the regional level should be the method of choice to quantify [¹¹C]befloxatone binding.

In summary, [¹¹C]befloxatone can reliably quantify MAO-A concentrations in human PET studies, and its preferred outcome measure should be V_T estimated by compartmental modeling.

DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

- 1 Tong J, Meyer JH, Furukawa Y, Boileau I, Chang LJ, Wilson AA *et al.* Distribution of monoamine oxidase proteins in human brain: implications for brain imaging studies. *J Cereb Blood Flow Metab* (2013) ; **33**(6):863–871
- 2 Leroy C, Bragulat V, Berlin I, Gregoire MC, Bottlaender M, Roumenov D *et al.* Cerebral monoamine oxidase A inhibition in tobacco smokers confirmed with PET and [11C]befloxatone. *J Clin Psychopharmacol* (2009) ; **29**(1):86–88
- 3 Zanotti-Fregonara P, Leroy C, Roumenov D, Trichard C, Martinot JL, Bottlaender M. Kinetic analysis of [11C]befloxatone in the human brain, a selective radioligand to image monoamine oxidase A. *EJNMMI Res* (2013) ; **3**(1):78
- 4 Zanotti Fregonara P, Leroy C, Rizzo G, Roumenov D, Trichard C, Martinot JL *et al.* Imaging of monoamine-oxidase A in the human brain with [11C]befloxatone: quantification strategies and correlation with mRNA transcription maps. *Nucl. Med. Commun.* (2014) In press