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In vivo localized 15N and 1H MRS in the hyperammonaemic rat brain at 9.4T

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1. Purpose

^{15}N MRS is an alternative approach to ^{13}C MRS for studying glutamate-glutamine metabolism. Moreover, the incorporation of ^{15}N into [5-^{15}N]Gln allows to measure glutamine synthetase activity directly and can provide a more straightforward interpretation than ^{13}C studies. Previous ^{15}N NMR studies under ammonia infusion used either in vivo ^{1}H or unlocalized ^{15}N spectroscopy (1), but never combined. Absolute quantification in these studies was done on in vitro brain extracts. Therefore, the goal of this study was to use in vivo localized ^{15}N MRS interleaved with in vivo ^{1}H MRS and to perform a direct absolute quantification of 5-^{15}N Gln and 2-^{15}N Glu/Gln in the same experiment.

2. Material and Methods

^{1}H and ^{15}N MRS data were acquired interleaved on a 9.4T system (Varian/Magnex Scientific) using 8 rats. $^{15}NH_4Cl$ solution was infused continuously for up to 10h (4.5mmol/h/kg) (1). ^{1}H spectra were acquired and quantified as described previously (2). ^{15}N unlocalized and localized spectra were acquired using the SIRENE sequence (3) (VOI=7x10x10mm^3, 256 averages); and quantified using AMARES and an external reference method (4). Due to the big chemical shift difference between 5-^{15}N Gln and 2-^{15}N Glu/Gln (~70ppm) the two ^{15}N signals were acquired separately in an interleaved mode using adiabatic excitation pulses with opposite frequency modulations.

3. Results

The increase in the total Gln pool at different time points during infusion was visible in the ^{1}H spectra (Fig. 1). The total Gln (0) concentration was 2.5±0.3 mmol/kg$_{ww}$, increasing to 15±3.3mmol/kg$_{ww}$ at the end of the infusion, which was in the range of previous studies (1). The 5-^{15}N Gln peak (-271ppm) was visible in the first and all subsequent scans, whereas the 2-^{15}N Gln/Glu peak (-342ppm) was observed after about 1.5h (Fig. 2). The concentration of 5-^{15}N Gln increased to 10.8±2.5mmol/ kg$_{ww}$ at the end of the infusion. The time courses of total Gln and 5-^{15}N Gln were highly reproducible in all rats.

4. Conclusion

We conclude that it is feasible to combine localized in vivo ^{15}N with ^{1}H MRS to measure total Gln, 5-^{15}N Gln and 2-^{15}N Glu+Gln under ammonia infusion in the rat brain. This technique allows a robust absolute quantification of total Gln, 5-^{15}N Gln and 2-^{15}N Glu/Gln in the same experiment.

5. References

[1]Kanamori K et al., Biochem J 1993;293:461. [2]Mlynarik V et al., J Magn Reson 2008;194:163. [3]Choi IY et al., Magn Reson Med 2000;44:387.[4] Gruetter R et al., J Neurochem 63:1377

Acknowledgements

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6. Mediafiles

Fig. 1

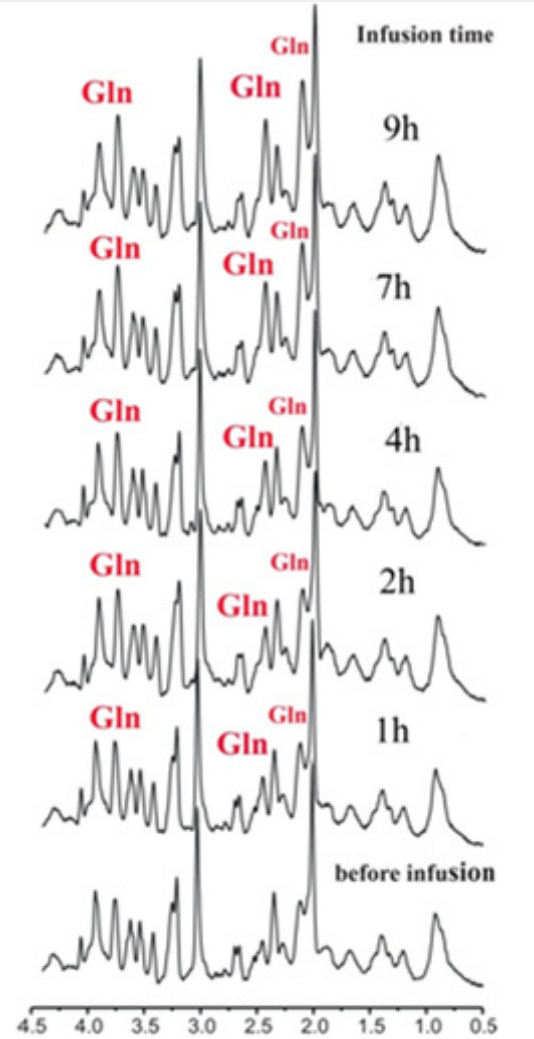

Fig 1. One series of *in vivo* ^{1}H spectra acquired at 9.4T in the rat brain.

Fig. 2

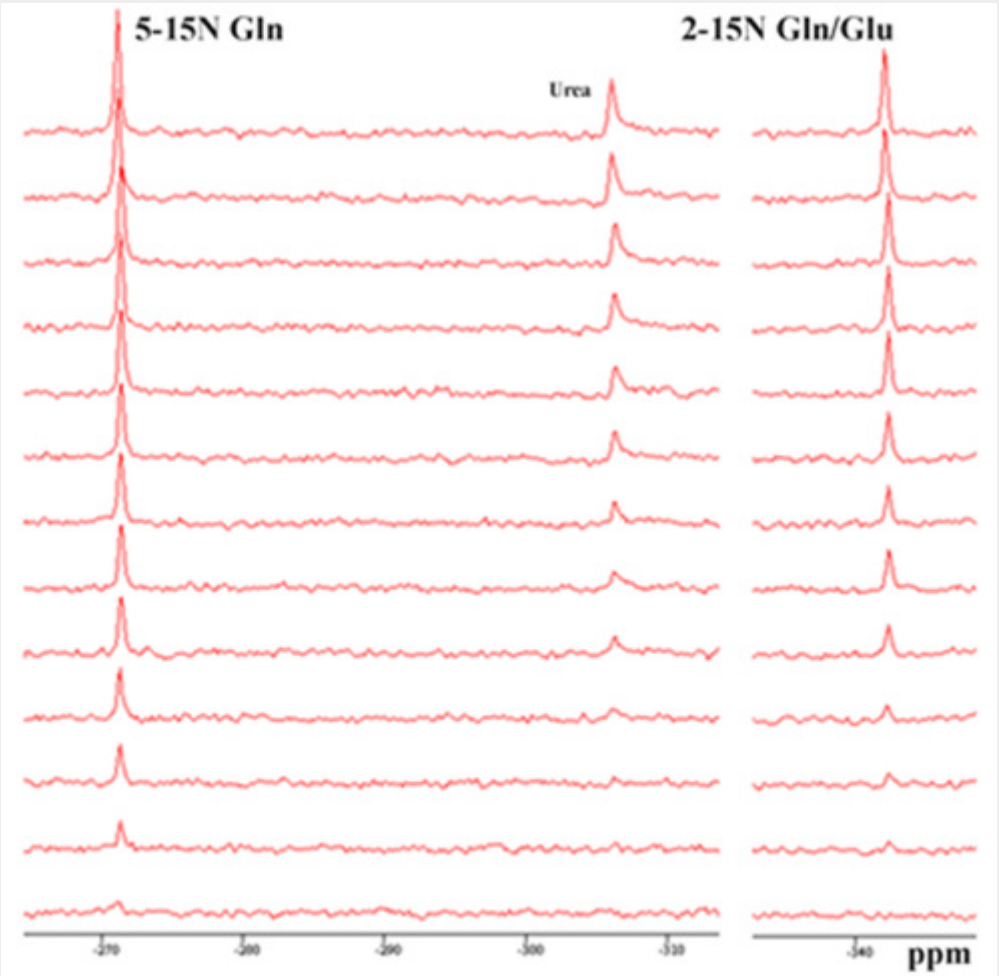

Fig. 2: A series of in vivo unlocalized ^{15}N spectra acquired at 9.4T in the rat brain at different time points. The ^{15}N chemical shifts were referenced to nitromethane.