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Glucose metabolism of the midline nuclei raphe in the brainstem observed by PET–MRI fusion imaging

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ABSTRACT

The brainstem contains various important monoaminergic neuronal centers, including the raphe nuclei which contain serotonergic neurons. The raphe nuclei, however, are not easily identifiable and located by conventional neuroimaging.

Methods: Fluorodeoxyglucose positron emission tomography (PET) and magnetic resonance imaging (MRI) were performed in seven healthy subjects using a new PET–MRI, which consists of a high-resolution research tomograph (HRRT) PET and 7.0 T-MRI. Glucose metabolism of raphe nuclei was semiquantitatively measured and identified along the midline brainstem region in vivo.

Results: Midline nuclei clustered in four groups appeared to be the raphe nuclei and could be clearly visualized; specifically, we identified the groups as the dorsal raphe, raphe reticularis centralis superior, raphe pontis, and raphe magnus group.

Conclusion: FDG imaging of the midline raphe nuclei in vivo could potentially be an important tool for investigating brain diseases as well as conducting functional brain studies in the context of sleep disorders, depression, and neurodegenerative disease.

Introduction

Since the development of positron emission tomography (PET) in the mid-1970s (Cho et al., 1976; Phelps et al., 1978), it has been possible to observe molecular changes and metabolic function of the human brain in vivo. More recently, PET has become increasingly popular for the diagnosis of cancer and tumors, especially with markedly improved resolution and increased availability of the novel radiotracers. PET has also become an important tool for the study of functional and disease states of the human brain, such as the subcortical areas that hitherto was unable to observe. With the development of brain-dedicated high-resolution PET, such as high-resolution research tomograph (HRRT) (Schmand et al., 1999; Wienhard et al., 2002), ultra-high-resolution brain imaging of cortical as well as subcortical areas and even subcortical monoaminergic nuclei became possible mainly due to the reduction of the partial-volume effect, one of the major stumbling blocks in the conventional PET for high-resolution brain imaging, especially in the brainstem. On another front, ultra-high-field magnetic resonance imaging (MRI), such as 7.0 T-MRI, also began to permit visualizing the human brain in vivo and to offer extensive detail of brainstem areas, such as the red nucleus and substantia nigra (Cho, 2009). These advances led us to develop a PET–MRI fusion system that combined two high-end imaging systems, HRRT-PET and 7.0 T-MRI, for the study of functional and metabolic activities of the brain in vivo, including the brainstem (Cho et al., 2008).

The combination of the functional and neuro-molecular imaging of HRRT-PET and high-resolution structural imaging capability of 7.0 T-MRI has opened a new avenue to study brain areas such as the brainstem once thought of as an invisible black box. Recently, the new PET–MRI system was successfully applied to study glucose metabolism of hippocampal substructures and thalamic nuclei of humans in vivo (Cho et al., 2010, 2011). Success in these studies encouraged us to conduct further research, such as in the brainstem, an intriguing and complex brain area that hosts most of the neuronal centers that secrete the major monoaminergic neurotransmitters, including serotonin. The simplest and perhaps most convincing study would involve the raphe nuclei, which is the center of the serotonergic neurons since they unmistakably reside along the dorsal midline of the brainstem starting from the uppermost part of the tagmentum and extending to the beginning of the medulla and are known to mediate numerous functions, such as sleep, appetite, and mood. However, MR images of the human brain in vivo usually have limited contrast and resolution for brainstem nuclei

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such as the raphe nuclei, and these images have consistently failed to visualize those nuclei. Given the development of serotonergic ligands such as the serotonin transporter ligand [^{11}C]3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile (^{11}C-DASB) and the serotonin 5HT1A ligand [carbonyl-^{11}C]N-(2-(1-(4-(2-methoxyphenyl)-piperazinyl) ethyl)-N-pyridinyl)cyclohexanecarboxamide (^{11}C-WAY100635), PET could measure serotonergic nuclei in the brainstem more directly and convincingly. However, the results of previous studies could not visualize the metabolic activities of the individual raphe nuclei mainly due to the limit of the resolution in the existing PET scanners (Ichise et al., 2003; Kim et al., 2006). The aim of the present study was to visualize and quantitate glucose metabolism in the various individual raphe nuclei by fusion imaging, using the newly developed brain-dedicated high-resolution PET–MRI (Cho et al., 2008, 2010, 2011).

Materials and methods

This newly developed PET–MRI fusion system consists of HRRT-PET and 7.0 T-MRI with a shuttle system through which two modality images are physically combined by the calibrated coordinates with high precision (Cho et al., 2008). Detailed specifications of the system are described in the Supplementary materials.

Ten healthy volunteers, eight men and two women (22.9 ± 1.73 years old), were recruited for the study. Among them, three participants (two men and one woman) were excluded due to their excessive motion during PET scanning. Each of the participants signed an informed consent form according to the protocol approved by the internal review board of Gachon University of Medicine and Science. A bolus injection of [^{18}F]fluorodeoxyglucose (^{18}F-FDG) (185 MBq) was given to each subject immediately before 7.0 T-MRI. MRI was conducted for 30 min, and after 10 min, PET imaging was implemented and completed in 30 min. T2*-weighted two-dimensional gradient-echo images were obtained by 7.0 T-MRI with the following parameters: repetition time (TR) 750 ms; echo time (TE) 21 ms; flip angle 30°; voxel size $0.18 \times 0.18 \times 1.5$ mm; number of slices, 17. During the PET scan, an additional transmission scan using cesium 137 (^{137}Cs) was also performed for attenuation correction. The PET image was reconstructed using the 3D-OP-OSEM algorithm (Hong et al., 2007). The reconstructed image had a matrix size of $256 \times 256 \times 207$ with $1.22 \times 1.22 \times 1.22$ mm^3 iso-voxel resolution. After the scanning, both images were automatically fused by the system, which was precalibrated with submillimeter precision.

For the PET glucose uptake evaluation, the standardized uptake value ratio (SUVR) was obtained by normalizing the uptake value of PET images over the uptake value of the cerebellum of each subject. Eight regions of interest (ROIs) were defined and drawn from the PET–MRI fusion images of each subject. Among the eight ROIs, four ROIs were the raphe nucleus groups, according to Naidich et al. (2009), and the rest consisted of four non-raphe ROIs, namely the thalamus, red nucleus, mammillary body, and inferior colliculus. The relative levels of glucose metabolism were compared in both the selected raphe and non-raphe nuclei. Finally, the SUVR of each ROI was obtained from the PET–MRI fusion image for the analysis.

Results

For the first time, using HRRT-PET and 7.0 T-MRI fusion imaging, we were able to visualize glucose uptake of well-separated clusters of the activities that appear to be the raphe nuclei (Figs. 1a–c). Several localized metabolic activity groups, which are likely to represent the mesencephalic raphe nuclei, were clearly observed in the brainstem by HRRT-PET and further identified by 7.0 T-MRI anatomical image. A unique feature of the serotonergic study is that the raphe nuclei are all located along the midline posterior-dorsomedial brainstem areas (Fig. 1d) and are distinctly identifiable. The first group (R1), including the dorsal nucleus raphe, was located in the upper midbrain area close to the inferior colliculus (landmark structures such as red nucleus and mammillary body further support that R1 includes the dorsal raphe). Dorsal raphe nuclei, however, were difficult to distinguish from other nuclei in the vicinity because the dorsal raphe is intermingled with the red nucleus, which has relatively higher activity than the dorsal raphe. The second group (R2) was located ventral to the inferior colliculus in the upper portion of the pons. The R2 group, also known as the nucleus reticularis centralis superior, consistently shows the highest level of glucose metabolism among the raphe nuclei groups. The third group (R3), located at the central and posterior aspect of the pons, appeared to correspond to the nucleus raphe pontis. As the smallest among the four raphe nuclei groups, R3 was not easily discernable in two out of seven subjects. The fourth group (R4) was found at the most posterior and inferior aspects of the pons and also at the junction point to the superior aspect of medulla. This group appeared to include the nucleus raphe magnus, nucleus raphe obscurus, and nucleus raphe pallidus.

The level of glucose metabolism in the raphe nuclei was found to be much lower than in most of the cerebral cortex, except in the cerebellar cortex, where activities are somewhat higher than those in the brainstem but generally do not reach those of the cerebral cortices (Fig. 1e). Within the vicinity of the raphe nuclei, there are several well-known landmark structures that verified our affirmation of the clusters as the raphe nuclei: the inferior colliculus, red nucleus, and mammillary body. These landmark structures showed relatively higher levels of metabolism in the areas of the brainstem and always with certainty thereby provided us an additional information on the relative locations of the raphe nuclei, especially the high-resolution images obtained from 7.0 T-MRI.

These observations were consistently reproducible for all the subjects as shown in Fig. 2a. Although the exact location of each raphe nucleus differed slightly between individuals, the general distribution pattern was very consistent. However, the individual differences resulted in the blurring of the image when the intersubject data were averaged. Nevertheless, the typical pattern of glucose metabolism in the brainstem area was well characterized even after averaging of the images. The spatially normalized PET images of those activity groups were also well matched among the subjects (see Fig. 2b).

Discussions

Using the new PET–MRI fusion imaging system, which consists of high-end PET (HRRT) and ultra-high-field MRI (7.0 T), glucose metabolism of several clusters of the individual brainstem raphe nuclei were clearly imaged and identified. Although MRI alone does not visualize the raphe nuclei because of low contrast, 7.0 T-MRI of the brainstem areas provided excellent images of several landmark anatomical structures from which it was possible to deduce the brainstem raphe nuclei groups. The results clearly identified the four groups of raphe nuclei in the brainstem area as described by Naidich et al. (2009). One of the unique features of the present study is that because the raphe nuclei are all located right in the midline of the brainstem, they are easy to locate, especially where the corresponding anatomy is clear due to a number of unmistakable landmark structures.

Although some previous rat or monkey studies (Fançois et al., 2010; Lyons et al., 1996; Skelin et al., 2008) using high-resolution autoradiography with ^{14}C-deoxyglucose reported glucose metabolism of the raphe nuclei, to our knowledge, this is the first report of clear visualization of the four groups of human raphe nuclei in vivo using FDG PET. Most of animal studies investigated the dorsal raphe and medial raphe only, except Skelin et al. (2008). Unlike our findings, they found that rats showed highest metabolism in the raphe pontine among raphe nuclei. It could be due to the difference between human and animal or due to the anesthesia applied to rats for experiment. In addition, Heiss et al. (2004) imaged subcortical nuclei of the human brain using FDG-PET with HRRT-PET, but the individual raphe nuclei were not specifically found in that study. Their major interest was to