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Introduction

Physical exercise such as running is executed through a sophisticated neural control system in the brain. Neural processing in the human brain plays crucial roles not only in the generation of motor outputs but also in the perception and integration of various sensory inputs. There are various methods as tools of functional neuroimaging, such as nuclear medicine techniques including positron emission tomography (PET) and single photon emission computed tomography (SPECT), and other imaging modalities such as functional magnetic resonance imaging (fMRI), near-infrared spectroscopy (NIRS), electroencephalography (EEG) and magnetoencephalography (MEG).

We have been utilizing PET for many years to measure the regional metabolic changes of the living human brain[1,2)] and skeletal muscles during exercise[3,4)]. PET has been a useful tool for measuring cerebral metabolic changes induced by exercise tasks. This is especially true for PET procedures that utilize the radio-labelled glucose analogue ($[^{18}F]$fluorodeoxyglucose: $[^{18}F]$FDG). The half-life of $[^{18}F]$FDG, approximately 110 min, is suitable for long observation ranging 30 to 60 min. The metabolic change is trapped, which enables the observation of the remaining metabolic "record" or "memory".

An activated regional brain activity is, in physiological condition, accompanied by increased demand for glucose and is immediately followed by dilation of brain capillaries that results in increased regional cerebral perfusion. The cerebral perfusion can be measured using and PET with radio-labelled water ($[^{15}O]H_2O$), although this technique is cumbersome and has some restrictions, where subjects have to exercise in the supine position during PET examinations because of the short half-life (approximately 2 min).

Then, PET with [^{18}F]FDG has a merit in observing daily human activities as they are in their natural circumstances[5]. We first applied this [^{18}F]FDG PET technique to human subjects during a running task in the upright posture[1] and during actual car-driving[6].

History of functional neuroimaging of exercise

PET has been used for measuring regional brain activity during or following exercise tasks using various radioactive pharmaceuticals such as [^{18}F]FDG and [^{15}O]H_2O. Regional cerebral metabolic changes induced by exercise have been examined in animals using autoradiography technique such as [^{14}C]deoxyglucose ([^{14}C]2-DG)[7,8]. [^{14}C]2-DG has been a useful tracer for exercise studies because it does not require the simultaneous scanning of subjects during an exercise task[9]. Using this technique, Sharp et al.[10] demonstrated an increase in glucose uptake in the cerebellar vermis of swimming rats. On the other hand, another study using free-running rats showed no selective activity in the cerebellar vermis but moderately increased glucose uptake for the entire cerebellum[11]. Thus, this autoradiography technique using [^{14}C]2-DG has been useful for exercise studies because it does not require simultaneous scanning of subjects during an exercise task[9]; The metabolic alteration is trapped, which enables the observation afterward. With this technique, data acquisition can be performed following exercise tasks. However, the [^{14}C]2-DG was not applicable to human activation studies because its very long half-life.

Later, human studies were also conducted in terms of brain perfusion. The first study on human brain activity during exercise was conducted by Herholz and coworkers[12]. In this study, subjects were examined during a riding task in the half-upright posture using the ^{133}Xe clearance method. Later, using PET with [^{15}O]H_2O, Fink and coworkers demonstrated the regional activation during and immediately after an ergometer task. They showed activation in the superomedial part of the motor cortex associated with leg and arm motion, which disappeared immediately following the cessation of the motor task[13]. In addition, they demonstrated that the lateral part of the motor cortex remained active possibly due to chest wall movement associated with post-exercise hyperventilation[13].

We first applied [^{18}F]FDG PET to healthy human subjects during a running task in the upright posture[1], and demonstrated augmented energy consumption in the parieto-occipital region during the task compared with the motor area. This was probably due to the higher energy consumption necessary for integrating multimodal sensory information. Our results also showed that frontal activity was lower during running than during resting. In addition, our group also examined whole-body energy (glucose) redistribution and how exercise affects this distribution[14]. Based on our work[1], Kemppainen and coworkers examined absolute glucose consumption in the human brain of healthy volunteers. They demonstrated that the glucose consumption in the human brain was clearly diminished in proportion to exercise strength.

Methodological aspects

In studies using [^{18}F]FDG, subjects are instructed to run for a total of 30 to 40 min after [^{18}F]FDG injection, with 10 to 15 min of exercise before injection. The amount of injected [^{18}F]FDG is approximately 40 to 80 MBq (1 to 2 mCi per subject) if a 3D data acquisition system is used. If a 2D system is used, 200 MBq [^{18}F]FDG (approximately 5 mCi) is needed for data acquisition to compensate for the lower sensitivity of the detector system. For [^{18}F]FDG injection, a catheter is usually inserted into an antecubital forearm vein. The plasma time-activity curve (pTAC) of subjects demonstrates that the plasma [^{18}F]FDG concentration is very high for the first 10 min or so after injection, and then gradually decreases. Therefore, it is recommended that exercise tasks be conducted during the first 30 min or so. With this in mind, [^{18}F]FDG PET can be an ideal technique for studies on exercise physiology by separating “a task phase” and “data acquisition phase”. This paradigm allows investigation of a totally free movement task assigned to subjects. With the [^{18}F]FDG PET technique, subjects can carry out any tasks, that is, not only running but any movement such as driving of a car or swimming[5,6]. PET scanning is initiated 40 min after [^{18}F]FDG injection since [^{18}F]FDG uptake in brain tissue reaches the plateau level at around 40 to 50 min post-injection. Our previous study suggested the presence of lateralization in muscular glucose metabolism used during upright running[1,5]. Although the temporal resolution of the [^{18}F]FDG PET technique is limited (just 30 to 60 min), it is this unique property that enables the application of this technique to observe human daily movement.

Results and discussion

Using [^{18}F]FDG PET technique, we have demonstrated the relative increase in glucose uptake in the temporo-parietal association cortex, occipital cortex, premotor cortex, primary sensorimotor cortex and the cerebellar vermis[1,5]. Relative reduction of glucose uptake was detected in the prefrontal cortex, temporal cortex, cerebellar hemisphere, brain stem, striatum. Mean values of global brain glucose uptake was relatively lower in runners than in resting controls[1,5]. Kemppainen and coworkers replicated the study and demonstrated significant reduction of regional glucose metabolic rate in all cortical regions in correlation to exercise intensity, especially in the dorsal part of the anterior cingulate cortex[2].

Interestingly, they also pointed out that exercise training could be associated with adaptive metabolic changes in the frontal cortex[2]. Thus, global and regional brain metabolic decline was observed using [^{18}F]FDG PET especially in the limbic and frontal regions[1,2,5]. The relatively low glucose uptake detected in the cerebellar hemisphere in our study was brought about by the adaptation due to the repetition of the same motor task[15]. We speculated that the frontal and limbic hypometabolism was associated with emotional changes in runners, including the phenomenon called "runner's high", a sensation of well-being and reduced anxiety during running[5,16]. Dietrich and Sparling reported that endurance exercise tended to impair prefrontal-dependent cognitive ability in healthy young male volunteers[17]. Based on these findings, Dietrich proposed a new theory, a "transient hypofrontality theory (THT)", where the prefrontal activity is suppressed indirectly due to the limitation in energy supply to the brain in the situation where enormous amount of energy is needed for execution of endurance exercise[18]. Interestingly, this theory explains well a neural mechanism regarding the mental health benefits of exercise[17,18].

In addition, the [^{18}F]FDG PET technique can be applied to functional neuroimaging studies of other movement tasks such as car driving. So far, neural correlates of car-driving have been studied using fMRI and PET techniques and the reproducibility of the findings has been demonstrated[19-22]. However, interestingly, all these neuroimaging studies have been using simulated car-driving tasks instead of actual car-driving task[19-22].

Conclusion

PET neuroimaging of daily movement is a relatively new research topic. An advantage of [^{18}F]FDG PET method is that subjects do not have to be scanned at the same time than during the exercise. We have demonstrated the feasibility of [^{18}F]FDG PET in monitoring brain activations induced by actual running in the upright posture. This technique supplies further evidence to support the positive aspects of exercise in the fields of sports physiology and psychology.

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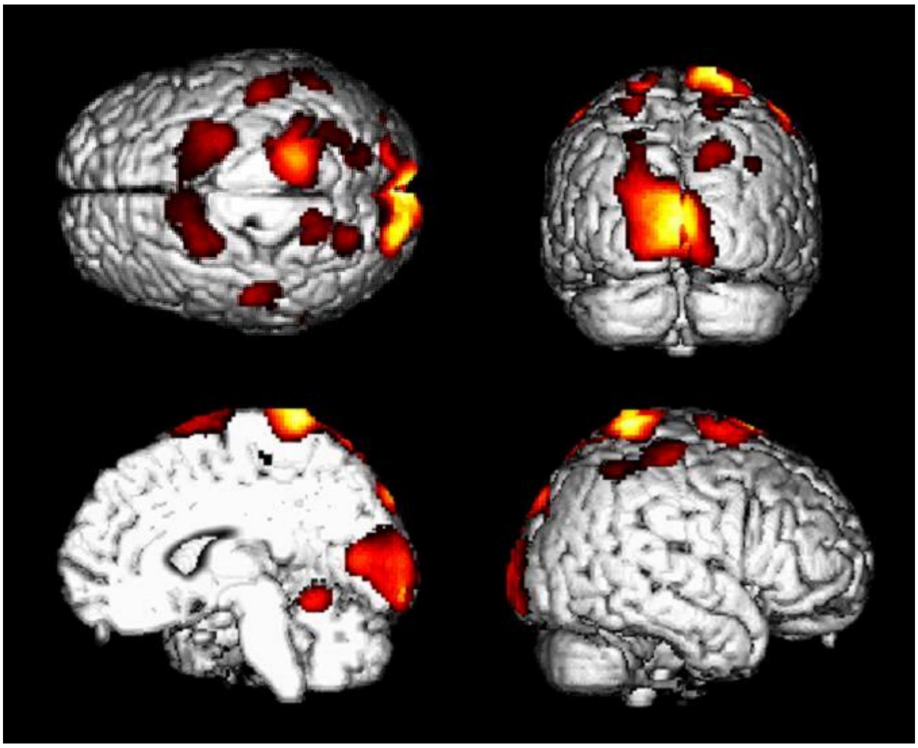

Figure 1. Results of [^{18}F]FDG PET study using a running task in the up-right posture in healthy volunteers.