POSITRON EMISSION TOMOGRAPHY AS A TOOL FOR STUDYING ALCOHOL ABUSE

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Positron emission tomography (PET) is an imaging technology that measures the concentration, distribution, and pharmacokinetics of radiotracers—molecules that are labeled with short-lived positron-emitting variants (i.e., radioisotopes) of chemical elements naturally found in the body. These radioisotopes can be attached to compounds involved in normal brain function and then injected into the blood stream. For example, radioactive carbon-11 (^{11}C) and fluorine-18 (^{18}F) can be used to label the sugar glucose, which is the brain's only energy source, and oxygen-15 (^{15}O) can be used to label water molecules, which can help measure blood flow in the brain. The signals emitted by these radiotracers then are measured using specific detectors. For example, for brain measurements, detectors arranged in a ring around the subject's head collect the data, which are then transferred to a computer and converted into a three-dimensional image of the brain. Because these measurements are noninvasive, the technology allows researchers to track biochemical transformations in the living human and animal body. PET is a highly sensitive method; it measures radioisotope concentrations in the nanomolar to picomolar range (10^{-9} to 10^{-12} M) (Schmidt 2002). Therefore, the technique can be used to label compounds that are of pharmacological and physiological relevance. These radiotracers then can be used to probe neurochemical and metabolic processes at the relevant physiological concentrations without perturbing the system that is measured.

To exert their effects on the brain, alcohol and other drugs (AODs) act on signaling molecules (i.e., neurotransmitters) in the brain as well as on the molecules on the surface of neurons (i.e., receptors) with which the neurotransmitters interact. (For more information on nerve signal transmission, neurotransmitters, and their receptors, see the article by Lovinger, pp. 196–214.) Specific compounds that selectively bind to such receptors, to the molecules that transport neurotransmitters back into cells, and to the enzymes that are involved in the synthesis or metabolism of neurotransmitters can be labeled for use as PET radiotracers. As a result, PET can be used to assess the metabolic and neurochemical actions of AODs and to evaluate the consequences of chronic AOD use (Volkow et al. 1997; Wang et al. 2000; Wong et al. 2003). Since its inception, PET has been used extensively to study the effects of AODs in human and nonhuman primates; however, the recent development of microPET technology has expanded its applications to research in rodents. In addition, increasing numbers of studies are using PET methodology to assess the involvement of genetic variations in individual genes (i.e., polymorphisms) in brain function and neurochemistry. This article specifically summarizes the role of PET as a tool for alcohol neuroscience research. The studies discussed are divided into those that assess the effects of alcohol on brain function (i.e., brain metabolism and cerebral blood flow) and those that assess its effects on neurochemistry.

PET Analyses of Brain Function

Indicators of brain function, such as cerebral blood flow, glucose utilization, and oxygen consumption, are the most common signals detected in functional brain-imaging techniques. These metabolic signals have been examined in a variety of disorders, primarily through the use of (^{18}F)-fluoro-2-deoxyglucose (FDG) as a radiotracer in PET imaging. Thirty-two years after its introduction, FDG still is the most widely used radiopharmaceutical for PET studies. This type of PET imaging allows the noninvasive observation of glucose utilization by different types of brain cells, including neurons and supporting cells known as glial cells (Magistretti and Pellerin 1996). In the brain, the sugar glucose is metabolized to lactate, which is a preferred energy source for neurons. Accordingly, glucose metabolism is a powerful indicator of brain function. FDG–PET imaging has the potential to detect very early brain dysfunction, even before neuropsychological testing yields abnormal results. In addition, the technique can be used to monitor treatment response and the effects of possible therapeutic intervention against the disease.

PET analyses using FDG to measure brain glucose metabolism and radiolabeled water to measure cerebral blood flow have been used to study the acute and chronic effects of alcohol in nonalcoholic control subjects, alcoholics, and people at risk of alcoholism (e.g., children of

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alcoholics). Other PET studies using FDG have examined alcohol's toxic effects on neurons (i.e., neurotoxicity) or gender-specific responses to alcohol. The findings include the following:

- Acute alcohol administration markedly reduced brain glucose metabolism throughout the whole brain, including the prefrontal cortex (Volkow et al. 2006) (see figure 1), whereas it increases cerebral blood flow in some brain regions, such as the prefrontal cortex (Volkow et al. 2007). In addition, it was shown that alcoholics displayed both a prefrontal modulation (i.e., reduced brain glucose) in the activity of cells using the neurotransmitter dopamine, combined with a profound decrease in dopamine activity (Volkow et al. 2007). These data suggested that interventions to restore prefrontal regulation and the dopamine deficit could be therapeutically beneficial in alcoholics (Volkow et al. 2007). Moreover, normally, brain metabolism and cerebral blood flow are coupled—that is, areas that show high brain metabolism also exhibit high blood flow and vice versa. Thus, these findings also suggest that alcohol dissociates this metabolic flow coupling.

- A recent FDG–PET study demonstrated abnormally low function of a brain region called the thalamus, which processes and relays information from other brain regions, in alcoholics suffering from acute alcohol-related hallucinations (Soyka et al. 2005).

- Alcoholics and normal subjects respond differently to an acute alcohol challenge, with the alcoholics showing a smaller behavioral response but larger decrease in brain metabolism than normal subjects (Volkow et al. 1993).

- Regional brain metabolic changes in response to treatment with the benzodiazepine medication lorazepam, which, like alcohol, enhances the activity of the neurotransmitter γ-aminobutyric acid (GABA), differed between alcoholic and control subjects. The findings likely indicate altered function of a certain type of GABA receptor (i.e., the GABA–BZ receptor) in alcoholics (Volkow et al. 1995). Indeed, the pattern of regional brain metabolic decrements seen with acute alcohol administration is similar to that observed after acute administration of lorazepam in healthy people, supporting the hypothesis that alcohol and benzodiazepines have a common molecular target for some metabolic effects (Wang et al. 2000).

- Studies measuring brain glucose metabolism or cerebral blood flow documented reduced activity in frontal and parietal cortical regions in alcoholics. This observation is consistent with findings from neuropsychological studies showing that alcoholics have deficits in executive function and attention, which are controlled by these brain areas. Overall, these studies strongly support the concept that alcoholism is associated with damage to the frontal and parietal lobes.

- Several studies have used imaging to probe the recovery of brain function after alcohol withdrawal. These studies found that the alcohol-related decreases in brain glucose metabolism partially recover in abstinent alcoholics, particularly during the first 16 to 30 days after withdrawal (Volkow et al. 1994).

Imaging studies also have addressed the influence of gender on the effects of alcoholism on the brain. It generally is believed that women are more vulnerable to alcohol's toxic effects than men. However, whereas male alcoholics have consistently shown reductions in brain glucose metabolism relative to control subjects, a PET study using ^{18}FDG in 10 recently detoxified female alcoholics reported no differences between alcoholics and control females (Wang et al. 1998). These results do not support the assumption that alcohol has greater toxic effects on the female brain, at least with respect to regional brain glucose metabolism. However, it should be noted that the severity of alcohol use in these female alcoholics was less than that of the male alcoholics previously investigated in PET studies. Therefore, studies in male subjects with moderately severe alcoholism are required to confirm gender differences in sensitivity to alcohol's effects on brain metabolism.

PET Analyses of Neurotransmitters and Receptor Binding

PET imaging also has been an effective tool in examining neurotransmitter systems associated with alcohol abuse and alcoholism (for a review of the various neurotransmitter systems affected by alcohol, see Koob 2003; Koob and Le Moal 2008). PET studies have shown that several neurotransmitters appear to mediate alcohol's reinforcing and addictive effects (Wang et al. 2000). Of these, dopamine is believed to play perhaps the most important role in mediating alcohol's reinforcing effects by acting on a brain circuit called the mesolimbic dopamine system[1] (Fowler and Volkow 1998). Researchers have used a plethora of radiolabeled compounds to examine various components of the dopamine system using PET analyses, including the following:

- [^{11}C]m-tyrosine, a radiolabeled variant of the amino acid tyrosine, which is the starting material for dopamine synthesis;

- [^{18}F]DOPA, a radiolabeled variant of a compound known as 3,4-dihydroxy-L-phenylalanine (L-DOPA), which is an intermediate product in dopamine synthesis;

- A molecule called [^{11}C]DTBZ (dihydroytetrabenzine), which helps measure the activity of the vesicular monoamine transporter (VMAT)—a transport protein that helps

[1] This brain circuit primarily involves two brain regions called the ventral tegmental area (VTA) and the nucleus accumbens (NAc). It plays a central role in reward, motivation, and reinforcement. Its activity also is controlled by certain areas of the prefrontal cortex.