Radioligands for Brain Imaging of the κ-Opioid System

The opioid receptor system is an essential part of the brain reward system, and the presence of μ-, ∂-, and κ-opioid receptors in the central nervous system is well documented (*1,2*). Understanding of opioid receptor availability and function, however, is based mainly on animal experiments. PET opens a unique access for the in vivo assessment of a biologic system such as the central opioidergic system in healthy volunteers and patients with neuropsychiatric disorders. So far, a seriously limiting step was the availability of highly selective tracers that assess an opioid receptor subtype, in particular, κ-opioid receptors. On pages 484–494 of this issue of *The Journal of Nuclear Medicine,* Talbot et al. (*3*) present excellent data on the preparation and imaging qualities of a selective ligand for the κ-opioid receptor. They show that GR103545, a stereotactic isomer of a potent κ-opioid receptor agonist, GR89696, displayed excellent brain penetration and uptake kinetics. The regional distribution of its binding potential was in accordance with the central distribution of κ-opioid receptors in primates and a promising specific-to-nonspecific equilibrium partition coefficient. Ligand binding was reduced to unspecific uptake in all examined brain areas by pretreatment with naloxone, a potent opioid receptor antagonist. This study is particularly promising in the light of current research on the opioid system in neuropsychiatric disorders. Two examples of this rapidly developing field will illustrate the potential usefulness of this new radioligand.

The central opioid system plays a role not only in heroin addiction but also in cocaine and alcohol dependence. Different drugs of abuse stimulate dopamine release in the ventral striatum, which includes the nucleus accumbens. Striatal dopamine release is stimulated by μ-opioid receptor activation, the center of origin of mesolimbic dopaminergic projections to the ventral striatum, and inhibited by striatal κ-opioid receptors (*4*). A subgroup of these κ-receptors is upregulated in chronic cocaine abusers (*5*). Moreover, chronic cocaine intake increases the expression of the transcription factor CREB (cyclic adenosine monophosphate–responsive element-binding protein) in the ventral striatum. CREB in turn activates gene expression of the endogenous opioid dynorphin, a potent agonist at κ-receptors (*1*). Dynorphin-mediated κ-receptor activation may thus represent a homeostatic mechanism that limits cocaine-induced dopamine release in the ventral striatum; however, during cocaine withdrawal, persistent κ-receptor activation may contribute to dysphoric mood states and thus increase the relapse risk. First rodent studies support the hypothesis that κ-receptor activation interferes with brain stimulation reward as measured with intracranial self-stimulation (*6*). In vivo brain imaging with radioligands such as GR103545 now provides a unique opportunity to assess the opioidergic system in drug-dependent humans, to examine the psychologic correlates of its functional state, and to develop new strategies to target drug effects and alleviate drug addiction.

Moreover, in vivo assessment of κ-opioid receptors may also indicate why some alcohol-dependent patients do not respond to naltrexone medication. Alcohol-preferring rodents displayed low central endorphin concentrations and a high availability of μ-opiate receptors in the ventral and dorsal striatum and prefrontal cortex (*2,7*). Central endorphin concentrations increased after alcohol intake (*8*) and may interact with elevated μ-opiate receptors in the ventral striatum, thus mediating the rewarding effects of alcohol consumption. In vivo PET studies with the μ-opiate receptor ligand carfentanil also showed elevated μ-opiate receptors in the ventral striatum of alcoholics and indicated that changes in the striatal and prefrontal availability of μ-opiate receptors are associated with alcohol craving (*9,10*). Conversely, blockade of μ-opiate receptors with naltrexone reduced the hedonic effects of alcohol intake (*11*) and the relapse risk among some but not all alcoholics (*11–13*). In vivo brain imaging of κ-opioid receptors in detoxified alcoholics may help to identify the neurobiologic correlates of naltrexone nonresponse and thus improve treatment of this most frequent psychiatric disorder among men living in industrialized countries.

The κ-opioid receptor has also been implied in Alzheimer's disease, Tourette's syndrome, and epilepsy (*14–16*). Furthermore, κ-receptor activation provided ischemic neuroprotection after transient ischemia in rats (*17*). It will be extremely interesting to compare neurologic and psychologic correlates of κ-opioid receptor function across these different neurologic and psychiatric disorders and to explore potential neuroprotective effects with molecular imaging.

Although the authors successfully prepared the tracer in the required high enantiomeric purity, labeling yield was low (*3*). Moreover, specific activity was not high, although pharmacologic effects were not observed or were to be expected. By use of ^{11}C-methyl iodide, both high radiochemical yields and

Received Sep. 13, 2004; revision accepted Sep. 14, 2004.

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high specific activities are usually obtained. However, that type of labeling procedure cannot be applied because in GR103545 that binding site is sensitive with respect to receptor binding. If the *N*-carbamoyl-group used in GR103545 is altered to an *N*-acyl-group or *N*-benzoyl group, the inhibitory concentration of 50% for binding at κ-ORS increased by a factor of 250 and 250,000, respectively (*18*). It thus remains a challenging task to improve the labeling procedure for GR103545 so that this promising radioligand is obtained in high labeling yields and specific activities.

Altogether, Talbot et al. (*3*) did an excellent job and substantially increased our possibilities for the in vivo assessment of central opioidergic function and dysfunction in health and in some of the most devastating diseases in the modern world.

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