1.1. Whole Body Dosimetry

1.1.1. Objective

Should the brain imaging studies prove to be successful, we will continue with whole body dosimetry studies. Preliminary dosimetry studies with [^{11}C]MePPEP have been performed in nonhuman primates, however these need to be continued in humans before further investigation of this novel tracer can continue. This study is known by Eli Lilly as "H6O-MC-GCEC."

1.1.2. Study Population

In the current protocol, we wish to evaluate [^{11}C]MePPEP in approximately 10 additional healthy subjects.

1.1.3. Design

The whole body dosimetry studies will consist of subject evaluation followed by a PET scan.

1.1.4. Outcome Measures

We intend to determine the whole body distribution of activity and thereby calculate radiation exposure to organs of the body.

2. INTRODUCTION/SCIENTIFIC RATIONAL

2.1. Background

The central cannabinoid receptor was discovered relatively recently (Matsuda et al 1990). It mediates the effects of the naturally occurring ligands (endocannabinoids), anandamide, noladin ether, virodhamine and 2-arachidonylglycerol, which are neurotransmitters and plant derived **Δ**-9- tetrahydronannabinol (THC, dronabinol), that is the primary psychoactive ingredient in *Cannabis sativa.*

The CB_1 receptor has widespread distribution in the body. CB_1 receptors are found in several brain areas (cerebellum, basal ganglia, hippocampus, cortex, hypothalamus, and pituitary gland), and in a variety of peripheral tissues, including adipose tissue, gastrointestinal tract, adrenal glands, sympathetic ganglia, heart, lung, liver, testis, eye, and urinary bladder. Endocannabinoids, such as anandamide and 2-arachidonylglycerol have a protective role in excitotoxicity. Altered endocannabinoids function is encountered in several neurological disorders (Parkinson disease, Huntington disease, and Alzheimer disease), psychiatric (schizophrenia) and eating disorders (anorexia nervosa and binge eating).

The CB_1 receptor is one of the most abundant neuromodulatory receptors in the brain and CB_1 receptor accounts for the effect of THC on memory, cognition, mood, sensory perception, appetite, pain, catalepsy, tremor, and decreased body temperature. In the monkey it was found in cortex, hippocampus, cerebellum, basal ganglia and amygdala, a high density of these receptors was observed in substantia nigra pars compacta, cerebellar Purkinje cells and the principal cells of hippocampus (Ong and Mackie 1999). In human brain some studies found the highest density of receptors in the substantia nigra pars reticulata (SNpr), globus pallidus, hipocampus and cerebellum

(Glass et al 1997; Herkenham et al 1990) whereas other (Mailleux et al 1992) found CB_1 receptors in caudate, putamen, all cortical layers and hippocampus and cerebellum. The receptor is found in presynaptic and postsynaptic locations. The CB_1 receptor belongs to the G protein-coupled receptor superfamily (Matsuda et al 1990). It is coupled in an inhibitory fashion to adenylate cyclase and both N- and P/Q-type calcium channels (Howlett 1985; Mackie and Hille 1992), and it has been shown to activate an inwardly rectifying potassium conductance (Mackie et al 1995). Inhibition of presynaptically located CB_1 receptor coupled to calcium channels was proposed to lead to decreased neurotransmitter release from axon terminals. At presynaptic sites CB_1 receptors function as retrograde messengers, which are released postsynaptically, travel backward across the synapses to suppress neurotransmitter release from axon, through inhibition of presynaptic calcium channels (Wilson and Nicoll 2002).

2.2. Development of a PET Ligand for CB_1 Receptors

Via a CRADA (Cooperative Research and Development Agreement) with Eli Lilly, we developed a novel PET radioligand for CB_1 receptors. [^{11}C]MePPEP was studied in approximately 8 scans in monkeys at NIH and showed excellent properties. In brief, brain uptake was high (~463+/- 116 %SUV at 46+/-22 min post injection), had a regional distribution appropriate for CB_1 receptor, washed out quickly, and could be displaced by agents selective for the CB_1 receptor. A representative time-activity curve is shown below in Figure 1.

We also studied the biodistribution of [^{11}C]MePPEP in two monkeys to estimate radiation exposure to organs of the body. Lisa Coronado of the NIH RSC approved our analysis of the imaging data. We found that the tracer caused relatively low radiation burden, with an Effective Dose of 24.5 mrem/mCi. Our proposed injected activity of 20 mCi would yield 490 mrem, well below the NIH annual limit of 5,000 mrem.

We will soon apply to the FDA for an IND to study [^{11}C]MePPEP. Of course, we will not begin any research without their approval.