## 3

ANALYSES OF PROSTAGLANDIN RECEPTORS BY IN VITRO AUTORADIOGRAPHY AND POSITRON EMISSION CT STUDIES IN MONKEY BRAIN.

Y.Watanabe*§, B.Långström†, Y.Watanabe§, N.Yumoto§, M.Hatanaka§, H.Hayashi§ and O.Hayaishi§
*Osaka Medical College, Osaka, §Hayaishi Bioinformation Transfer Project, Kyoto, and †Uppsala University, Sweden.

Prostaglandin(PG)s exert various neurophysiological functions in the central nervous system(CNS). We investigated the localization of PG receptors in the monkey and rat brains by in vitro autoradiography. The study showed a close relation between the localization of PG bindings and the known functions of PGs, and indicated the novel roles in CNS such as the modulatory role of $PGD_2$ in the olfactory stimulus-response in the olfactory bulb. To extend the study for the higher brain functions and dynamic aspects, we attempted to perform PET studies using the C-11-labeled PGs. By developing the synthetic conditions, we first succeeded in the syntheses of C-11-methyl (Me) and C-11-ethyl esters of $PGD_2$ and $E_2$ and C-11-Me of various other PGs. PET studies were performed by injecting C-11-Me's of $PGD_2$ and its inactive epimer $9\beta$-$PGD_2$ to Rhesus monkey. Although the clearance curves of the radioactivity in the blood and the radioactivity taken up into the temporal muscle were similar between both experiments, the uptake of the radioactivity into the brain using labeled $PGD_2$-Me was much higher than that using $9\beta$-$PGD_2$-Me.

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## 4

ASSESSMENT OF BENZODIAZEPINE RECEPTORS IN THE HUMAN BRAIN WITH PET

H.Shinotoh,O.Inoue,K.Suzuki,T.Yamasaki, T.Tateno. Division of Clinical Research, National Instite of Radiological Sciences, Chiba.

The recent development of the appropriate ligands and the technique of labelling them with high specific activity have made it possible to visualize the neuroreceptors with positron emission tomogarphy.

The in vivo study of receptors with PET require ligands with the following characteristics;

(1) highly permeable to the blood-brain barrier.
(2) remains unmetabolized in the brain during experiments and its metabolites in the peripheral blood do not pass through the blood-brain barrier.
(3) having high affinity and highly specific to a receptor.
(4) having high ratio of specific binding to non-specific biding in the brain.
(5) can be suitably labelled with a positron emitter in a short time.

We have chosen Rol5-1788 (Flumazepil) as a ligand for the study of benzodiazepine receptor in the brain, which has the characteristics described above. Carbon-11 labelled Rol5-1788 has been synthesized by reacting Rol5-5528 with 11C-CH3I, using automated synthesis system. Specific activity of 11C-Rol5-1788 varied from 1 to 3 Ci/umol at the end of synthesis. We have been studying benzodiazepine receptors in the brain with PET since October 1984.

The rapid and high uptake of 11C activity was observed in the human brain following intravenous injection of 11C-Rol5-1788 and 11C activity approached a near-equibrium state within 10 minutes. The saturation experiment with large amount of unlabelled Rol5-1788 showed that more than 80% of the total radioactivity in the cerebral cortex was that of specific binding ligands (more than 90% in animal experiments).

Thus assuming that 11C-Rol5-1788 reaches a equbrium state within 10 minutes and all the radioactivity is that of specificifically bound ligands after 10 minutes, we can make an assessment of potential (Bmax·Kd-1). The ratio between the radioactivity in the cerebral cortex and that of unmetabolized 11C-Rol5-1788 is related to the binding postential of benzodiazepine receptors.

The goals of the neuroreceptor study with PET are as follows;

(1) elucidation of the physiological roles of the receptors.
(2) study of the chemical abnormalities of various neuropsychiatric disorders.
(3) investigation of the effects of various drugs on the receptors and the pharmacokinetics at the receptor sites.

With regard to the above points, the results of the benzodizepine recptor study with PET at NIRS will be presented.