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First delineation of 5-HT_{1A} receptors in human brain with PET and [^{11}C]WAY-100635

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Abstract

The selective 5-HT_{1A} receptor radioligand, [^{11}C]WAY-100635 {[^{11}C]*N*-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-2-pyridyl)cyclohexanecarboxamide}, has been injected intravenously into healthy male volunteers and studied by PET (positron emission tomography). The results provide the first delineation of 5-HT_{1A} receptors in living human brain and demonstrate the potential to use [^{11}C]WAY-100635 for the study of central 5-HT_{1A} receptors in patients with psychiatric and neurological disorders and for the investigation of the pharmacology of drugs acting on the central nervous system.

Keywords: 5-HT_{1A} receptor, human; PET (positron emission tomography); [^{11}C]WAY-100635

5-HT_{1A} receptors have been studied extensively since their identification in brain tissue. These receptors play a fundamental role in controlling the tone of central serotonin (5-hydroxytryptamine, 5-HT) neuronal activity since, in addition to acting as postsynaptic receptors in the hippocampus and several other brain regions, they are the main somatodendritic autoreceptors mediating negative feedback control of the serotonergic system. The regional distribution of 5-HT_{1A} receptors in brain is similar in all examined species, including human (Palacios et al., 1987). Changes in 5-HT_{1A} receptor function are possibly involved in the aetiology of several psychiatric disorders, such as anxiety, depression, dementia and schizophrenia. Here we report the first delineation of central 5-HT_{1A} receptors in living human brain using positron emission tomography (PET) with a new radioligand, ^{11}C-labelled WAY-100635 [*N*-2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-2-pyridyl)cyclohexanecarboxamide] (Pike et al., 1995a,b; Hume et al., 1994; Mathis et al., 1994).

WAY-100635 is the first silent, potent and selective antagonist for 5-HT_{1A} receptors. Recently, it has been shown that the labelling of WAY-100635 with positron-emitting carbon-11 ($t_{1/2} = 20.4$ min) at high specific radioactivity provides the first effective radioligand for the detection of 5-HT_{1A} receptors in rodents (Pike et al., 1995a,b; Hume et al., 1994) and in monkey (Mathis et al., 1994) in vivo.

In this study, we have used PET to measure the regional distribution of radioactivity in brain at different times after intravenous injection of [^{11}C]WAY-100635 (6 mCi containing 10 μg of unlabelled WAY-100635) into a healthy male volunteer. Transaxial scans were obtained parallel to the orbito-meatal line and co-registered to MRI images in the same subject. The summed slices obtained from 20–90 min after injection show a distribution of radioactivity (Fig. 1) which closely matches the distribution of 5-HT_{1A} receptors seen in human brain in vitro. High uptake was seen in entorhinal cortex, frontal cortex, hippocampus and insula and low uptake in thalamus, hypothalamus, basal ganglia and cerebellum. The latter showed the lowest uptake

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and is known to be devoid of 5-HT_{1A} receptors (Palacios et al., 1987). The ratio of radioactivity in receptor-rich medial temporal cortex to that in cerebellum is 3.1 from 20 min after injection. Corresponding ratios for receptor-rich insula and cingulate are 2.7 and 2.0, respectively. High uptake was also seen in the brain stem, which probably represents binding of the radioligand to 5-HT_{1A} autoreceptors in the raphe nuclei. These data are replicated in 4 other healthy male volunteers.

At present there is no highly selective 5-HT_{1A} receptor antagonist that is approved for human use and hence it has not been possible to pre-block the binding of [^{11}C]WAY-100635 to brain 5-HT_{1A} receptors in humans to provide direct evidence of the receptor selectivity of radioligand binding. In one subject given the partial agonist, buspirone (30 mg orally), at 1 h before intravenous administration of [^{11}C]WAY-100635 the ratio of radioactivity in medial temporal cortex to that in cerebellum was reduced to 1.9 at 20 min after injection; further detailed studies are in progress to establish whether this reduced ratio is due to lower specific or higher non-specific binding. However, the uptake of [^{11}C]WAY-100635 into monkey brain is known to be blocked substantially by high doses of 8-OH-DPAT [8-hydroxy-2-(di-*n*-propylamino)tetralin], the prototypic selective 5-HT_{1A} receptor agonist (Mathis et al., 1994). This finding, the excellent selectivity expressed by WAY-100635 for 5-HT_{1A} receptors in vitro and in rodents ex vivo (Hume et al., 1994; Pike et al., 1995a,b; Laporte et al., 1994), and the well-defined distribution of radioactivity that we have ob-

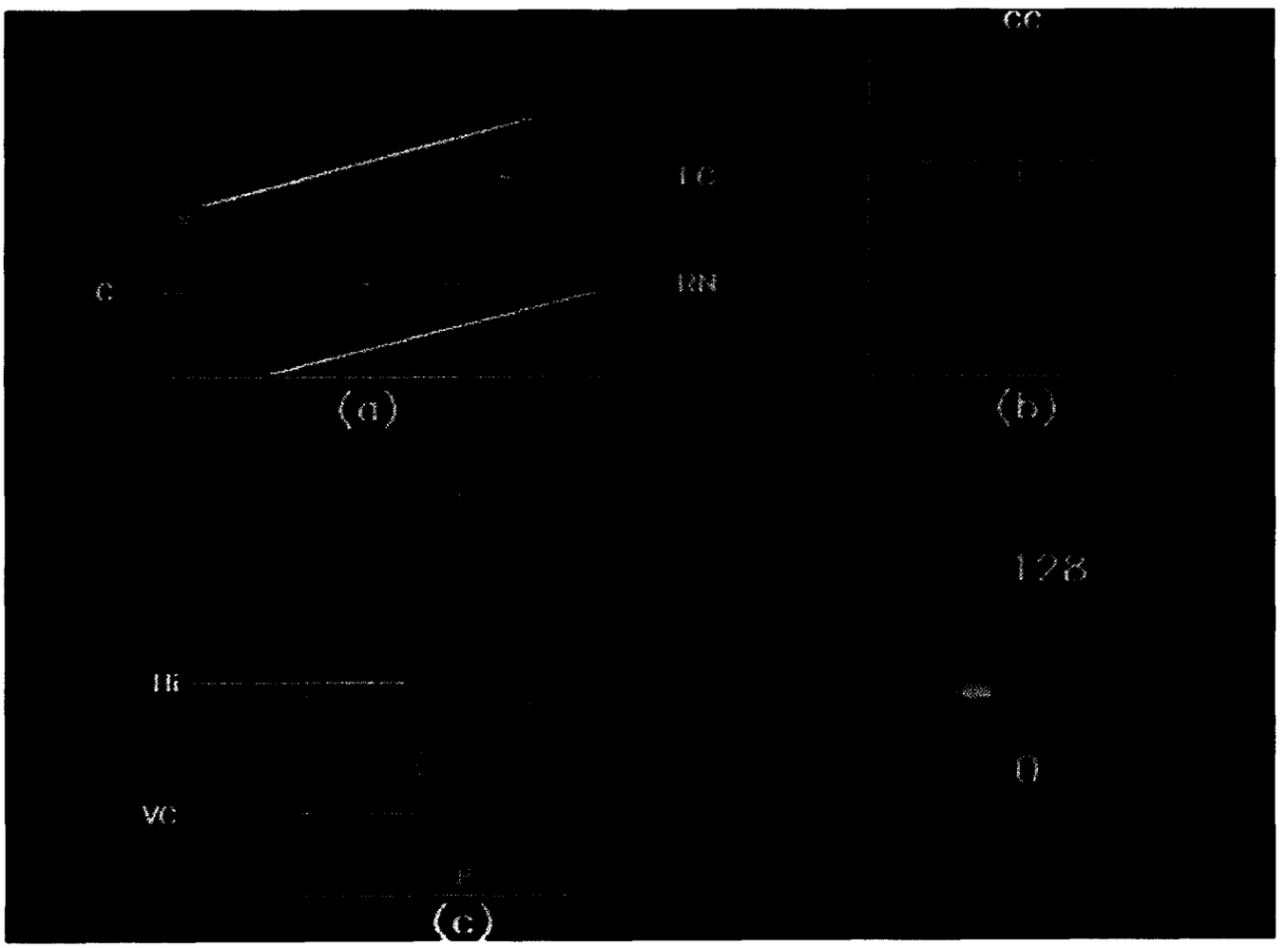

Fig. 1. Sagittal (a), coronal (b) and transverse images (c) of [^{11}C]WAY-100635 binding in human brain co-registered onto an MRI scan from the same subject. A and P denote anterior and posterior, respectively. White continuous lines show the field of view of the PET camera in the *Z*-axis. The yellow dotted line indicates the level of the transverse slice which passes through the medial temporal region. Labelling in the brain stem at the level of the raphe nuclei is seen in the sagittal and coronal images (just below the yellow dotted line and labelled RN in panel (a). Other brain regions are identified as C (cerebellum), FC (frontal cortex), GC (cingulate gyrus), Hi (hippocampal formation) and VC (visual cortex). The colour scale refers to grey level pixel intensity for the summed radioactivity counts, recorded from the PET camera from 20 to 90 min after injection of [^{11}C]WAY-100635.

served together assure that [^{11}C]WAY-100635 binds with high selectivity to 5-HT$_{1A}$ receptors in human brain.

The further development and validation of [^{11}C]-WAY-100635 as a radioligand, including the analysis of labelled metabolites in plasma and the mathematical modelling of kinetic data to provide receptor binding parameters are in progress. This should enable any anomalies in central 5-HT$_{1A}$ receptor populations in patients with psychiatric and neurological disorders to be detected and investigated. PET and [^{11}C]WAY-100635 may also serve as an important tool for the investigation of the pharmacology of drugs acting on the central nervous system, such as the major antidepressants, which in animal studies produce changes in the sensitivity of 5-HT$_{1A}$ receptors.

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