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

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Abstract

The 5-HT_{1A} receptor antagonist, WAY-100635 [*N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl) cyclohexanecarboxamide], was labelled in its carbonyl group with carbon-11 ($t_{1/2}$ = 20.4 min), injected intravenously into healthy male volunteers and studied with positron emission tomography (PET). The acquired data provide exquisite delineation of 5-HT_{1A} receptors in brain, with the ratio of radioactivity uptake in receptor-rich regions, such as medial temporal cortex, to that in receptor-devoid cerebellum reaching 25 by 60 min after radioligand injection. Application of biomathematical modelling to the data revealed high values (7.8) for binding potential, a measure of B_{max}/K_D, in receptor-rich regions. Only very polar radioactive metabolites were present in plasma, a finding consistent with the low level of nonspecific binding seen in cerebellum. [*carbonyl*-^{11}C]WAY-100635 is concluded to be far superior to the previously reported [*O-methyl*-^{11}C]WAY-100635 as a radioligand for PET studies of 5-HT_{1A} receptors in human brain.

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

WAY-100635 (*N*-(2-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-*N*-(2-pyridyl) cyclohexanecarboxamide) is the first potent and selective antagonist for 5-HT_{1A} receptors (Cliffe, 1993; Fletcher et al., 1993). Recently, we reported the first delineation of 5-HT_{1A} receptors in human brain by positron emission tomography (PET) using WAY-100635, labelled with carbon-11 ($t_{1/2}$ = 20.4 min) in its *O*-methyl position, as radioligand (Pike et al., 1995a). In these studies the ratio of radioactivity uptake in a receptor-rich receptor region, such as medial temporal cortex, to that in cerebellum, which is devoid of receptors (Palacios et al., 1987), was about 3 at 20 min from intravenous injection of radioligand. Previously, Mathis et al. (1994), using the same radioligand in a PET study of rhesus monkey, had obtained a value of ~6 for the ratio of radioactivity in receptor-rich frontal cortex compared to that in cerebellum. We have established that [*O-methyl*-^{11}C]WAY-100635 is rapidly metabolised in humans (Osman et al., 1995). A main radioactive metabolite has been identified as the descyclohexanecarbonyl analogue of [*O-methyl*-^{11}C]-WAY-100635, namely [*O-methyl*-^{11}C]WAY-100634. This radioactive metabolite represents 25% of the radioactivity in plasma at 60 min after the injection of [*O-methyl*-^{11}C]-WAY-100635 in humans, while more polar radioactive metabolites represent 70%.

WAY-100634 is known to have high affinities for 5-HT_{1A} receptors and α_1-adrenoceptors in vitro. Furthermore, [*O-methyl*-^{11}C]WAY-100634 is avidly taken up by brain after injection into rats (Pike et al., 1995b), suggesting that this radioactive metabolite could contribute significantly to nonspecific and even receptor-specific binding in human brain in PET studies of [*O-methyl*-^{11}C]WAY-100635. We therefore considered that an increase in signal contrast might be obtained in PET studies of 5-HT_{1A} receptors in human brain by placing the radiolabel in a position that would avoid the formation of radioactive

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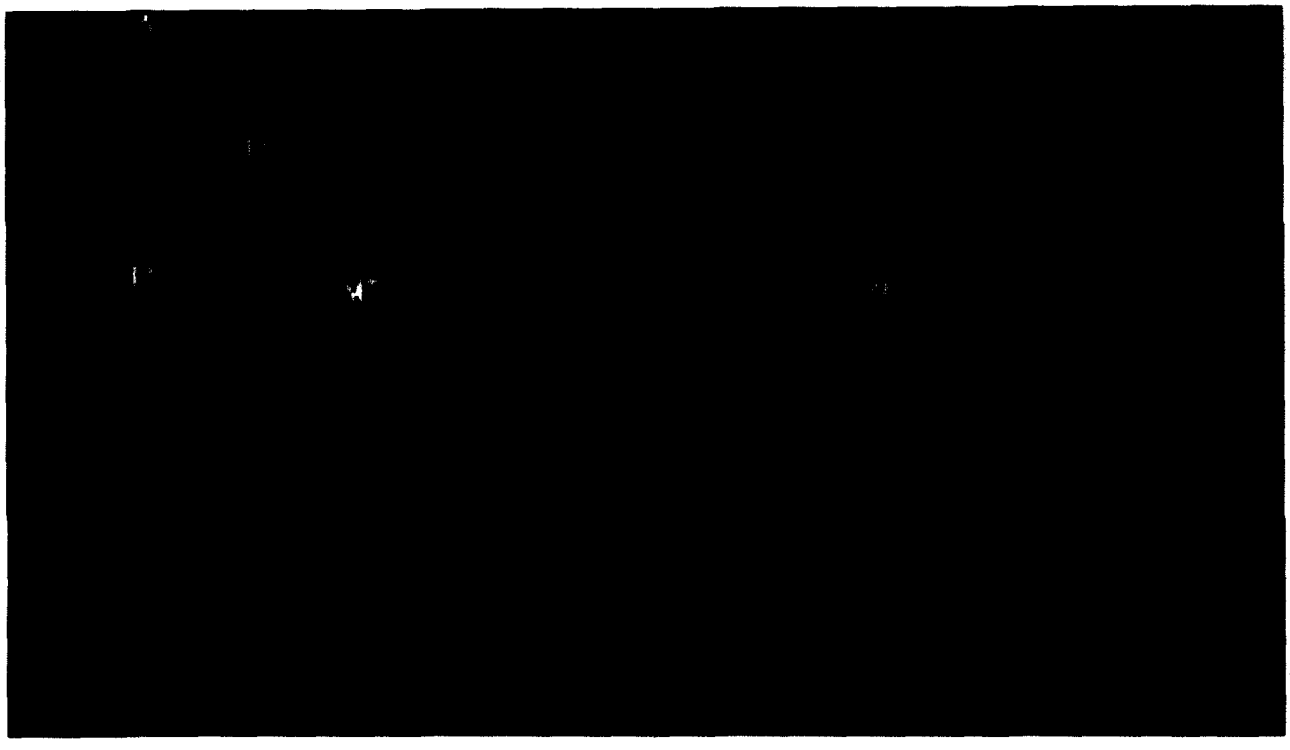
WAY-100634. Hence, we labelled WAY-100635 in the carbonyl position (Pike et al., 1995b) and studied the uptake of radioactivity in brain after intravenous injection into two human volunteers.

After injection of [*carbonyl*-^{11}C]WAY-100635 (270 MBq; specific radioactivity 75 GBq/μmol) into a male human volunteer, transaxial PET scans were obtained parallel to the orbito-meatal line. The summed data from 20



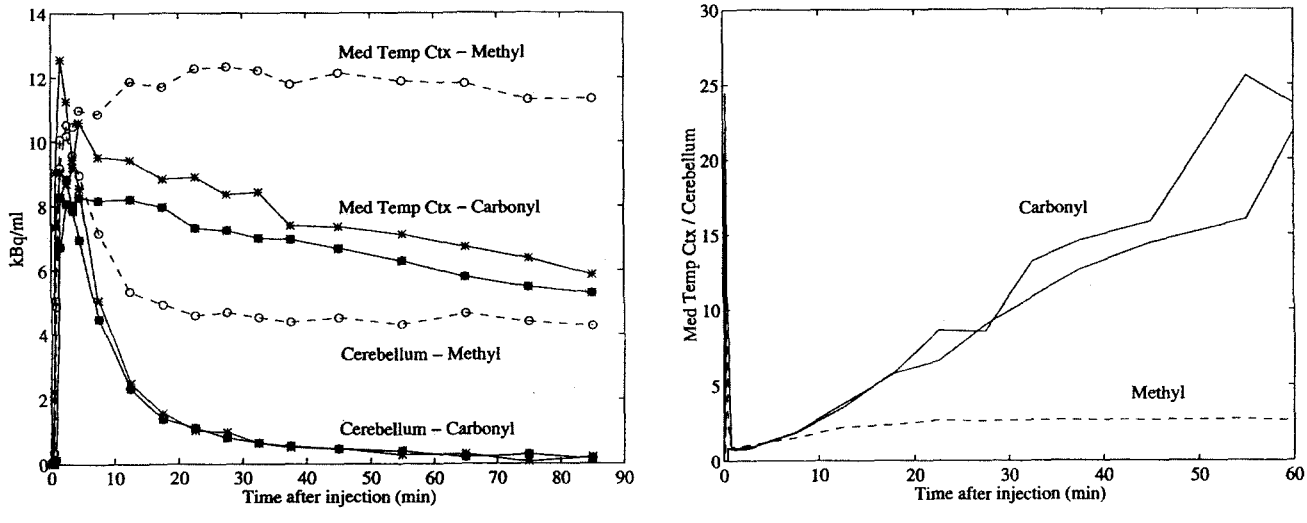


Fig. 1. Top panel: transverse contiguous images of [^{11}C]WAY-100635 binding in human brain (A, P, L and R are anterior, posterior, left and right respectively). Brain regions identified are C (cerebellum), VC (visual cortex), MT (medial temporal cortex), I (insula) and RN (raphe nuclei). The colour 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. Note the very low level of radioactivity in the 5-HT$_{1A}$ receptor-devoid cerebellum. Bottom left panel: decay-corrected time-radioactivity curves for medial temporal cortex and cerebellum in three healthy volunteers, one injected with [*O-methyl*-^{11}C]WAY-100635 (broken lines) and the other with [*carbonyl*-^{11}C]WAY-100635 (solid lines). Time-radioactivity curves are normalised for body weight (70 kg) and for injected dose (25.9 MBq). Note the dramatic decrease of nonspecific binding in the cerebellum with the carbonyl label. Bottom right panel: ratio of radioactivity counts in medial temporal cortex to cerebellum in three healthy volunteers, one injected with [*O-methyl*-^{11}C]WAY-100635 (broken line) and two others with [*carbonyl*-^{11}C]WAY-100635 (solid lines).

min to 90 min after injection show exquisite delineation of 5-HT_{1A} receptors with high uptake in receptor-rich regions, such as medial temporal cortex (Fig. 1). The raphe nuclei are also sharply defined. Kinetic analysis of the data shows that the ratio of radioactivity uptake in receptor-rich medial temporal cortex to that in cerebellum reaches the remarkably high value of 25 by 60 min after injection (Fig. 1). This value arises from the very low level of radioactivity in cerebellum, showing that this radioligand gives much lower nonspecific binding than [*O-methyl*-^{11}C]WAY-100635 (Fig. 1). The analysis of plasma has shown that the new radioligand is rapidly metabolised but only to very polar radioactive compounds. These are not expected to enter brain; nor are they expected to be pharmacologically active since they are most probably [^{11}C]cyclohexanecarboxylic acid and simple derivatives. Thus, the plasma input function is clearly defined. A reference tissue compartmental model (Lammertsma et al., 1996) was applied to the acquired scan data and yielded values for binding potential, a measure of B_{max}/K_D, in receptor-rich regions. For medial temporal cortex the values for the two subjects were both 7.8.

[*carbonyl*-^{11}C]WAY-100635 is clearly preferable to [*O-methyl*-^{11}C]WAY-100635 for use as a radioligand for PET studies of 5-HT_{1A} receptors in human brain. The high sensitivity, absence of labelled metabolites in brain, and amenability to biomathematical modelling of [*carbonyl*-^{11}C]WAY-100635 render it a powerful new tool for the investigation of 5-HT_{1A} receptors in neuropsychiatric disease and for the pharmacological investigations of psychoactive drugs with PET.

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