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THE SYNTHESIS OF [*O-METHYL*-^{11}C]VENLAFAXINE : A NON-CLASSICAL, FAST-ACTING ANTIDEPRESSANT

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Summary

As part of our program to develop PET tracers for the 5-HT reuptake site, venlafaxine, a non-classical, fast-acting antidepressant, was selected as a candidate for labelling with ^{11}C for *in vivo* evaluation. [*O-methyl*-^{11}C]venlafaxine was produced by the alkylation of O-desmethyl venlafaxine with [^{11}C]methyl iodide followed by HPLC purification and formulation. Radiochemically pure [*O-methyl*-^{11}C]venlafaxine was obtained in a 30 ± 5 % decay corrected radiochemical yield and a specific activity > 50 GBq / μmol (1.4 Ci / μmol) at the end of synthesis. For a typical production starting with 46 GBq (1.3 Ci) [^{11}C]CO_2, 5.2 GBq (140 mCi) [*O-methyl*-^{11}C]venlafaxine was obtained as a sterile, formulated solution in a synthesis time of 30 min (counted from EOB).

Key words:^{11}C, antidepressants, 5-HT reuptake, PET, venlafaxine

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Introduction

The development of tracers labelled with positron emitting radionuclides (eg. ^{11}C, ^{13}N, ^{15}O and ^{18}F: half-lives 20.4, 2, 10 and 110 min respectively) in conjunction with positron emission tomography (PET) has enabled the non-invasive study of normal and abnormal neurotransmission and metabolism in humans *in vivo*. An important target for future research is the study of depression, a disease which is expected to seroiusly affect 18 out of 100 people during their life span.[1] The monoamine theory of affective disorders proposes that depression is related to abnormal serotonergic neuro-transmission. This theory is supported by the fact that depressed patients often improve their symptomatology upon treatment with selective serotonin reuptake inhibitors. The study of the 5-HT reuptake site in normal and depressed subjects, therefore, may aid our understanding of the pathophysiology of the disease.

At present however, there are no ideal PET ligands availiable for the study of serotonin reuptake sites, although the recently reported pyrroloisoquinoline derivative [^{11}C]McN-5652 appears to have potential.[2-5]

In view of this situation we have selected a number serotonin uptake inhibitors as candidates for labelling in order to evaluate their potential as PET tracers of the 5-HT reuptake site *in vivo*. The ^{11}C-labelling of one such compound, venlafaxine, [6-8] a non-classical, fast-acting antidepressant is reported here.

Experimental

General - ^{11}C-CO_2 was prepared by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction using a nitrogen gas target and 16 MeV protons produced by the GE Medical Systems PETtrace

cyclotron at Aarhus University Hospital. O-Desmethyl venlafaxine hydrochloride (WY-45233) (**1**) and venlafaxine hydrochloride (WY-45030) (**2**)were obtained from Wyeth-Ayerst Research laboratories, Princeton, New Jersey, USA.

Hydriodic acid (57 %, unstabilised), triethylamine (TEA), sodium hydride (60 % oil dispersion), anhydrous dimethyl formamide (DMF) and HPLC grade ethanol were purchased from Aldrich. Anhydrous tetrahydrofuran (THF) and lithium aluminium hydride (LAH) were obtained from Merck. All above reagents were used without further purification.

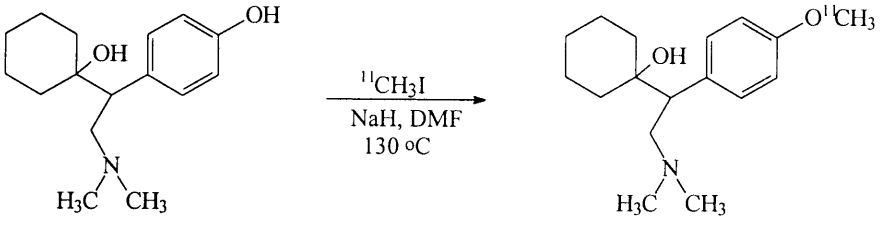
LAH (ca. 500 mg portions) was transferred, under argon, to 5 cm^3 vials which were subsequently sealed and stored in a desiccator under argon until required. A fresh saturated (ca. 1 M) solution of LAH was made before each experiment by the addition of ca 5 cm^3 anhydrous THF to the vials containing LAH under an inert atmosphere.

The labelling procedure, including preparation of ^{11}C-methyl iodide, alkylation, semi-preparative HPLC purification, rotary evaporation, formulation and sterile filtration was performed using a fully automated system.[9]

Semi-preparative HPLC was performed using a Perkin Elmer model 200 isocratic pump equipped with a 5 cm^3 injection loop and connected in series with a Spherisorb 5-ODS (250 x 10.0 mm, 5 mm) column (column A), an Applied Biosystems 759A variable UV detector (l = 270 nm) and a radiodetector of in-house design. Analytical HPLC was performed using a Perkin Elmer model 250 binary pump equipped with a 20 µl injection loop and connected in series with a Spherisorb 5-ODS (250 x 4.6 mm, 5 mm) column (column B), an Applied Biosystems 759A variable UV detector (l = 270 nm) and a radiodetector of in-house design.

[^{11}C]Methyl Iodide - [^{11}C]Carbon dioxide was purged form the target in a stream of nitrogen gas and trapped on 4 Å molecular sieves. On heating, the ^{11}C-CO_2 was released and passed through a solution of LAH (300µl) in a stream of nitrogen gas. On completion of ^{11}C-CO_2 transfer, the THF was evaporated, 1 cm^3 hydriodic acid was added and the vessel was heated at 160 °C to form ^{11}C-methyl iodide.[10,11]

[O-methyl-^{11}C]Venlafaxine (**2**) - [^{11}C]Methyl iodide was distilled in a stream of nitrogen gas to a reaction vial containing 1 mg O-desmethylvenlafaxine (**1**) and 1.5 mg sodium hydride (60% oil dispersion) dissolved in 300 µl DMF. After heating for 5 min at 130 °C, the crude product was purified using column A, using ethanol : 5 mM TEA (80 : 20) as eluent at a flow rate of 5 cm^3/min. The fraction containing the ^{11}C-venlafaxine (**2**) (Rt = 8.9 min) was evaporated to dryness, formulated in a buffered saline solution and passed over a 0.22 µm filter into a sterile vial. The radiochemical purity and product identity were determined by analytical HPLC using column B with ethanol:5mM TEA (95:5) as eluent at a flow rate of 2 cm^3/min.



1 **2**

Scheme 1. The synthesis of [*O-methyl*-^{11}C]venlafaxine

Results and Discussion

The synthesis of [*O-methyl*-^{11}C]venlafaxine was achieved by the alkylation of O-desmethyl venlafaxine with [^{11}C]methyl iodide (Scheme 1). ^{11}C-Methylation of **1** in DMF at 130 °C for 5 min, using NaH as base, produced **2** as the major product (> 90 %). The only other radiolabelled component in the crude product corresponded to unreacted [^{11}C]methyl iodide.

Reverse-phase semi-preparative HPLC was used to purify the ^{11}C-venlafaxine (Figure 1). The labelling precursor (**1**) and unreacted ^{11}C-methyl iodide (eluting at 4.5 and 2.7 min, respectively) were well separated from ^{11}C-venlafaxine which eluted at 8.9 min. The radioactive peak corresponding to **2** was collected and the fraction evaporated to dryness under reduced pressure. The product which was formulated in buffered saline and passed over a 0.22 μm filter into a sterile vial was found to be sterile and pyrogen

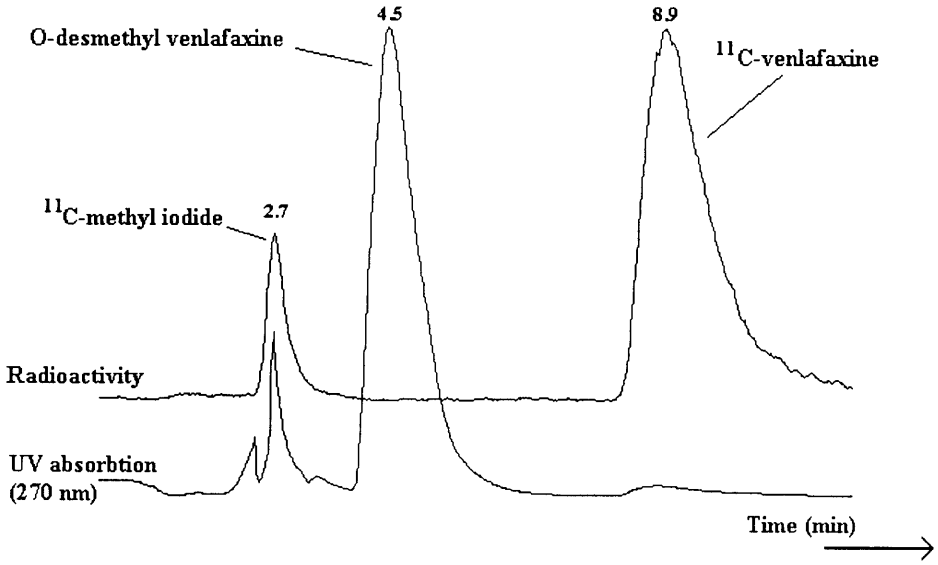


Figure 1. A typical semi-preparative HPLC chromatogram obtained from the purification of [*O-methyl*-^{11}C]venlafaxine

free. Radiochemically pure [*O-methyl*-^{11}C]venlafaxine was obtained in a 30 ± 5 % decay corrected radiochemical yield and a specific activity > 50 GBq /μmol (1.4 Ci / μmol) at the end of synthesis.

For a typical production starting with 46 GBq (1.3 Ci)[^{11}C]CO_2, 5.2 GBq (140 mCi) [*O-methyl*-^{11}C]venlafaxine was obtained in a synthesis time of 30 min (counted from EOB). Analytical HPLC showed the radioactive product to co-elute with an authentic sample of venlafaxine. No detectable levels of the labelling precursor **1** were found in the formulated product.

Conclusions

Radiochemically pure, high specific activity [*O-methyl*-^{11}C]venlafaxine can be produced in sufficient quantities for *in vivo* biodistribution studies. PET investigations are currently in progress to determine the suitability of ^{11}C-venlafaxine as a tracer for the 5-HT reuptake site. These results will be presented elsewhere.

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