SYNTHESIS, CHROMATOGRAPHY AND TISSUE DISTRIBUTION OF METHYL-^{11}C-MORPHINE AND METHYL-^{11}C-HEROIN

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SUMMARY

^{11}C-Morphine was prepared by methylation of normorphine with $^{11}CH_3I$. Acetylation of this compound yields heroin. The radiochemical yield is 9% for morphine and 4% for heroin at a specific activity of 1.63 mCi/μmole. Synthesis time including purification by hplc is 18 min for ^{11}C-morphine and 36 min for ^{11}C-heroin, respectively. The tissue distribution of both these compounds was determined in rats at different times after an i.v. injection. The main accumulation of activity is in the small intestine, followed by kidney and liver. Little activity was detected in the brain.

Key Words: Carbon-11, Morphine, Heroin, Animal Experiments

INTRODUCTION

Many of the pharmacological effects of morphine and heroin are known to be centrally mediated. Therefore we thought that one of these compounds might be a useful tool for tomographic and metabolic studies of the brain when labelled with a positron emitting nuclide like carbon-11 ($T_{1/2}$ = 20.3 min).

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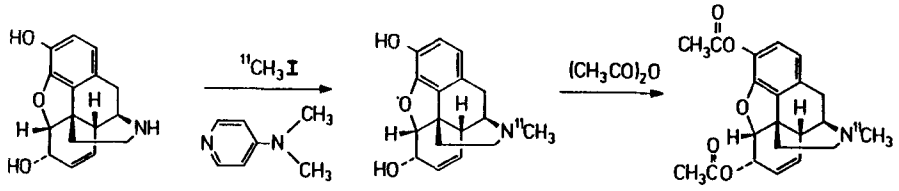
Morphine distributes unequally over the different regions of the brain, as shown by Mulé and Woods (1), but the absolute amount of radioactivity found in the brain is only a minute fraction of the dose. Since the diacetyl derivative of morphine, namely heroin, is more lipophilic than morphine, it is consequently taken up by the brain to a larger extent, as shown by Oldendorf et al. (2). Therefore, it should also be the better imaging agent. As a measure of the attainable concentration in brain, the highly potent morphine agonist etorphine yields a brain concentration of 75% of the dose ratio (3), i.e. 1.3 µg/kg at a dose of 1.7 µg/kg.

We decided to label morphine in the N-methyl-group, since this is the only position that can be conveniently labelled with carbon-11. The label will not be easily lost by metabolic N-dealkylation; it is known that only about 5 per cent of a morphine dose is dealkylated to yield normorphine (4).

EXPERIMENTAL

Normorphine was prepared according to Rapoport and Look (7). Practically carrier-free $^{11}CH_3I$ was prepared according to Marazano et al (8).



A typical preparation of ^{11}C-morphine and ^{11}C-heroin runs as follows:

t = 0 min — After transferring "carrier-free" $^{11}CH_3I$ (9.15 mCi) into a solution of 1 mg of normorphine and 1 mg 4-dimethylaminopyridine in 2 ml ethanol, this mixture is heated at 120°C for 10 min. The solution is evaporated to dryness using a rotary evaporator.

t = 13 min — The residue is taken up in 1 ml of 0.2 N aqueous NH_3 and injected onto a hplc-column (LiChroSorb Si 60 10 µ, 50x0.4 cm) via a sample valve. At a flow rate of 3 ml/min using 0.2 N aqueous NH_3 as eluent, morphine elutes with a retention time of 1.9 min.

t = 18 min — The ^{11}C-morphine peak is collected and evaporated to dryness as above. Yield: 849 µCi ≙ 9.3% (decay corrected).

t = 19 min — The ^{11}C-morphine is taken up in 1 ml acetic anhydride and heated at 120 °C for 5 min. The solution is evaporated to dryness as above.

t = 25 min — The residue is taken up in 1 ml 0.2 N aqueous NH_3 and subjected to hplc (conditions see above). The retention time of heroin is 4.4 min.

t = 32 min — The ^{11}C-heroin peak is collected and taken to dryness.

t = 36 min — Radiochemical yield: 376 µCi ≙ 4.1% (decay corrected)

Mass : 25 µg (110 µCi)

Specific activity : 1.63 mCi/µmole

Since normorphine is rather poorly soluble in ethanol, the reaction has to be carried out in a rather dilute solution.

Omitting the dimethylaminopyridine leads to a drastic reduction in yields. Addition of carrier methyl iodide to the reaction mixture does not improve the radiochemical yield. During preparation of $^{11}CH_3I$, about 0.1 - 0.3 µmole of non-radioactive CH_3I are generated, probably from athmospheric CO_2; therefore, morphine and heroin are not carrier-free.

The hplc conditions (see Table 1) were selected to yield a salt-free residue of ^{11}C-morphine or ^{11}C-heroin, even though the resolution between excess normorphine and ^{11}C-morphine is worse under these conditions than in the presence of salts in the eluent (9).

Table 1. Chromatographic data*

Compound	k'
morphine	0.93
normorphine	3.07
heroin	4.02
4-dimethylaminopyridine	> 6.0

*column: LiChroSorb Si 60, 10µ, 50 cm x 0.4 cm
eluent: 0.2 N NH_3 in water
flow: 3 ml/min

For administration to rats, the ^{11}C-morphine or ^{11}C-heroin was taken up in 1 ml isotonic saline and filtered through a 0.22 µm Millipore filter to yield a sterile solution suitable for injection.

ANIMAL EXPERIMENTS

Throughout the study male Wistar rats with body weights ranging from 360-530 g were employed. Between 0.1 and 0.3 ml of the ^{11}C-morphine or ^{11}C-heroin solutions were injected into the tail vein of lightly ether-anesthetized animals.

Animals were killed by bleeding after anesthetizing them with ether. The organs were removed, blotted dry, weighed, and counted in a well-type counter using a NaI(Tl)-scintillation detector.

The measured count rates were normalized. The count rate per g of organ weight (cpm/g) was divided by the injected dose (cpm per g body weight) to yield the enrichment in various organs.

Table 2. Tissue distribution of ^{11}C-morphine at different times after i.v. injection (n = number of animals)

	Time after administration (min)					
Organ	10(n=4)	20(n=4)	30(n=3)	40(n=3)	50(n=2)	70(n=2)
blood	0.44	0.31	0.32	0.29	0.22	0.21
heart	1.12	0.95	1.83	0.45	0.42	0.84
lung	1.39	1.21	1.17	0.86	0.56	0.58
liver	2.12	2.10	1.74	1.72	1.09	0.97
spleen	1.90	2.06	2.31	2.00	1.78	1.33
kidney	5.26	4.62	3.56	3.56	1.97	1.46
pancreas	1.40	0.94	1.80	0.68	0.75	0.30
testes	0.14	0.12	0.21	0.19	0.17	0.20
brain	0.09	0.17	0.19	0.16	0.14	0.08
small intestine	13.32	20.58	7.69	8.77	7.11	2.09

Values are expressed as cpm/g organ weight divided by dose (cpm/g body weight).

Table 3. Tissue distribution of ^{11}C-heroin at different times after i.v. injection (n = number of animals)

	Time after administration (min)				
Organ	10(n=2)	20(n=2)	30(n=2)	40(n=2)	50(n=1)
blood	0.29	0.44	0.28	0.27	0.25
heart	0.92	0.99	0.65	1.75	0.52
lung	1.70	1.48	1.01	1.35	0.76
liver	1.48	2.27	1.31	2.09	1.20
spleen	1.73	4.71	2.29	2.86	2.09
kidney	4.29	6.45	3.20	4.86	2.30
pancreas	1.52	1.17	1.57	0.46	1.57
testes	0.10	0.23	0.14	0.28	0.32
brain	0.25	0.47	0.24	0.24	0.43
small intestine	10.68	10.84	11.38	6.45	5.02

Values are expressed as cpm/g organ weight divided by dose (cpm/g body weight).

DISCUSSION

Data on the pharmakokinetics and tissue distribution of morphine and heroin are rather scarce in the literature (10-13). The data show a rather low concentration of morphine in the central nervous system, whereas significant amounts of morphine are found in both liver and kidney (10,12,13). About 75% of a morphine dose are

excreted in the 24 hr urine (10), whereas only small amounts are excreted via the bile. The analgesic effect of morphine has been correlated to its brain concentration (11), but the correlation turned out to be complex. In short, analgesic action declines more rapid than brain concentration.

As far as we know, there are no data concerning the tissue distribution of heroin in animals.

The results presented in Tables 2 and 3 consistently show that the largest amount of radioactivity is bound by the small intestine (not its contents); this binding (up to 40% of the dose in small intestine) may account for one of the major side-effects of opiate narcotics, namely obstipation. Furthermore, the organs of metabolism and excretion, namely liver and kidney, contain large amounts of radioactivity, which corresponds well with literature data (14) stating that morphine suffers a first-pass effect of about 30% in the liver.

Rather disappointingly, the brain concentration of ^{11}C-heroin turned out to be less than could be expected concerning the data of Oldendorf et al. (2). The maximum enrichment of radioactivity from ^{11}C-heroin in the brain was 0.61, which is about three times that recorded for ^{11}C-morphine.

As heroin is rather unstable in hydroxylic solvents and only attains rather low brain concentrations, the use of this compound as a tool for brain imaging is not possible. The even lower concentrations of ^{11}C-morphine make this compound even less useful for that purpose.

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