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Apiaceae sub *Umbelliferae*
Arecaceae sub *Palmae*
Asteraceae sub *Compositae*
Brassicaceae sub *Cruciferae*
Clusiaceae sub *Guttiferae*
Fabaceae sub *Leguminosae* (including Mimosoideae = *Mimosaceae*, Caesalpinioideae = *Caesalpiniaceae* and Papilionoideae = *Papilionaceae* = Fabaceae sensu stricto)
Hypericaceae sub *Guttiferae*
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Research Articles

A Highly Specific O-Methyltransferase for Nororientaline Synthesis Isolated from Argemone platyceras Cell Cultures

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Abstract

A highly specific new enzyme, S-adenosyl-L-methionine: (6-O-methyl-norlaudanosoline)-5′-O-methyltransferase which catalyses the formation of nororientaline from 6-O-methyl-norlaudanosoline and SAM was discovered, partially purified, and characterized. *Argemone platyceras* cell suspension cultures served as enzyme source.

Introduction

Tetrahydroisoquinoline biosynthesis in plants involves a number of O- and N-methylation steps [e.g. 1] of norlaudanosoline, the first precursor in the pathway. In a previous communication, we have described the isolation of a first specific O-methyltransferase. In *Argemone platyceras* cell suspension cultures this enzyme methylates predominantly the 6-O-position of (S)- as well as (R)-norlaudanosoline, mediating the transfer of a methyl-group from S-adenosyl-L-methionine to NLS [2]. During the purification of this enzyme, a second enzymatic activity was discovered which utilises 6-O-methyl-NLS to introduce a second methyl group in the 5′-position of the molecule to yield nororientaline. Again SAM serves as a methyl group donator. Nororientaline is a principal immediate precursor of papaverine in *Papaver somniferum* [1] and is also undoubtedly converted to orientaline by N-methylation. Orientaline itself has been isolated from opium poppy [3] and is metabolized in *Papaver orientale* via orientalinone to isothebaine [4]. Therefore nororientaline can be considered as a specific precursor of a number of isoquinoline alkaloids in higher plants. This report describes the partial purification and characterization of a new enzyme which was designated S-adenosyl-L-methionine: (6-O-methyl-norlaudanosoline)-5′-O-methyltransferase.

Abbreviations: NLS = Norlaudanosoline; SAM = S-Adenosyl-L-methionine; SAH = S-Adenosylhomocysteine.

Material and Methods

Argemone platyceras cells were cultivated as described previously [2]. Chemicals used were essentially those described in the preceeding communication [2]. The new enzyme, described here, was purified through steps 1–4 as described previously [2]. However, the enzyme was eluted from hydroxyapatite columns at fractions 56–65 in contrast to the previously described NLS-6-O-methyltransferase which was eluted between fractions 43 and 54. Enzyme assays were carried out as follows: (R, S)-6-O-methyl-norlaudanosoline (0.3 mM), SAM-^{3}H (10000 cpm, 0.1 mM), KPO_4^{2-}-buffer, pH 7.5 (130 mM) were incubated in a total volume of 150 µl at 35° C for 45 min. The reaction was terminated by the addition of 200 µl Na_2CO_3-buffer (1 M, pH 9.5). The methylated product was extracted by adding 400 µl isoamylacohol and shaking for 45 min. After centrifugation for 5 min. in an Eppendorf centrifuge, 200 µl of the organic phase were transferred to scintillation vials and counted. A blank value of about 10 % (obtained by assay mixtures containing either no enzyme or no substrate), had to be subtracted from all incubation mixtures. Recovery of the methylated product was 92 % under these conditions.

The products were separated and identified by HPLC using a Nucleosil-SA-column (25 mm × 3.2 mm i.d.) and 0.5 M ammonium phosphate : methanol (70:30) as a solvent system. Retention time of the potential products were: norisoorientaline, 7.14 min.; nororientaline, 8.20 min.; norprotosinomenine, 8.84 min.; norreticuline, 10.94 min.

Preparative isolations were done using the above incubation mixture × 100. The reaction product was extracted by ethylacetate and purified twice by thin layer chromatography (Si-gel; solvent systems: 1) chloroform : methanol : acetic acid : water = 18:6:3:0.3; 2) acetone : chloroform : diethylamine = 5:4:1). Mass spectra were determined in a Finnigan MAT 44S instrument.

Results and Discussion

During the purification of the 6-O-methyltransferase evidence was obtained that its reaction product

Table I

Purification protocol for the 5′-O-methyltransferase from *A. platyceras* cell suspension cultures (125 g fwt)

Purification step	Volume (ml)	Total activity (pkat)	Protein (mg/ml)	Spec. activity (pkat/mg)	Yield	Purification factor
Crude extract	236	4647	1.10	17.97		1
$(NH_4)_2SO_4$ precipitation	23	5733	10.02	24.9	100	1.4
Gelfiltration	69	5703	0.22	375.5	99.48	20.9
DEAE chromatography	35	1127	0.07	506.5	19.65	28.2
Hydroxyapatite	12	327.7	0.038	718.8	5.7	40.0

Table II

Some characteristics of (6-O-methylnorlaudanosoline)-5′-O-methyltransferase from *A. platyceras* cell cultures

Characteristics	5′-O-methyltransferase
Molecular weight	47.000
pH-optimum	7.5
Temperature optimum	35° C
K_M for 6-O-methylnorlaudanosoline	0.4 mM
K_M for SAM	0.05 mM
K_i for SAH	0.034 mM

Table III

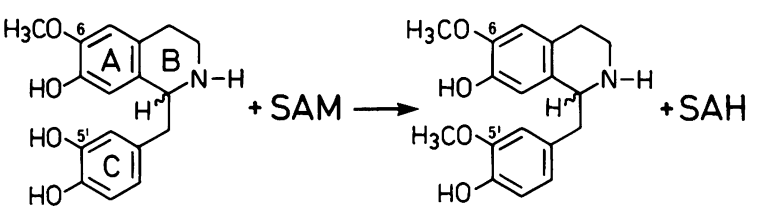
Substrate specifity of 40-fold purified 5′-O-methyltransferase using SAM as methyl group donator

Substrate	pkat/mg	%	Product of reaction
(R, S)-6-O-methyl-norlaudanosoline	314	100	Nororientaline
(R)-Norlaudanosoline	0	0	–
(S)-Norlaudanosoline	0	0	–
(R, S)-Laudanosoline	0	0	–

is transformed by the introduction of a second methyl group in the presence of excess SAM and crude enzyme preparations. The two enzymes involved are clearly separated by chromatography on hydroxyapatite. The enzyme was partially purified by using (R,S)-6-O-methyl-norlaudanosoline as substrate. As shown in Table I the enzyme could be recovered with 6 % yield. Purification was about 40-fold.

The characteristic properties of the enzyme are listed in Table II. The enzyme has a half life of 33 hrs at 30° C and retains full enzymatic activity in the presence of 0.05 % NaN_3 at 4° C after 4 weeks. The enzyme is, however, completely inactivated by freezing even in the presence of 30 % glycerol. The enzyme is inhibited completely by Fe^{3+} and Hg^{2+} ions at 5 mM concentration and is strongly inhibited by 5 mM p-chloromercuribenzoate (84 %), N-ethylmaleimide (82 %), and 10 mM jodobenzoic acid (79 %). This indicates that SH-groups are present at the active center of the enzyme. Similar findings have been reported for the unspecific *meta* and *para* directing catechol-O-methyltransferases from plant origin [5]. The general properties of the enzyme, described here, are very similar to the previously described norlaudanosoline-6-O-methyltransferase.

The substrate specifity of the 5′-O-methyltransferase was of considerable interest. 18 substrates were tested for their ability to accept methyl groups from SAM catalysed by S-adenosyl-L-methionine: (6-O-methyl-norlaudanosoline)-5′-O-methyltransferase. None of the phenols, phenylpropanoids, flavonoids, coumarins, and biogenic amines tested, served as substrates. Out of 12 different isoquinoline alkaloids tested [2] only (R,S)-6-O-methyl-norlaudanosoline was methylated. Surprisingly neither (R) or (S)-norlaudanosoline nor (R, S)-laudanosoline served as a substrate (Table III) which shows a hitherto unique substrate specifity of an O-methyltransferase in plant kingdom [6]. Since the 6-O-methyl-norlaudanosoline used was a racemate, it is not known whether either



6-O-Methylnorlaudanosoline Nororientaline

of the two stereoisomers is preferentially methylated. As shown by HPLC (retention time 8.20 min.) and mass spectroscopy ($[M+1]^+$ 316, 100 %, measured with dci), the reaction product of the enzyme was unequivocally nororientaline. As shown in Fig. 1, the new enzyme therefore exclusively methylates the 5′-position of 6-O-methyl-norlaudanosoline.

Using $^{14}CH_3$-SAM as one substrate and this novel enzyme as catalyst it was possible to synthesize 5′-$^{14}CH_3$-nororientaline with excellent yields. Using callus of *A. platyceras*, feeding experiments with the labelled substrate showed that nororientaline was extensively metabolized by *Argemone*, yielding several alkaloids which are now being investigated. This finding demonstrates that the new enzyme is of physiological importance in the plant tissue.

Our results confirm previous findings [1, 2] that 6-O-methylation clearly precedes methylation at C-7 and methylation at ring C within the reticuline/orientaline pathway.

In addition the results obtained on the specific NLS-6-O-methyltransferase [2] and especially the 5′-O-methyltransferase described here clearly demonstrate that O-methylation precedes N-methylation.

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