Docking study of the precursor peptide of mastoparan onto its putative processing enzyme, dipeptidyl peptidase IV: a revisit to molecular ticketing

Feng-Yin Li
Mastoparan: A Bee poison
Sequence of prepromelittin

Arrows mark the peptide bonds cleaved by chymotrypsin (C) or partial hydrolysis (PH). It means 11 dipeptides were cut off from the precursor repeatedly. This action is called molecular ticketing.

Kreil et al., 1980
Mastoparan B processing

MKSTILILFTAFIALLGFFGMSA   EALADPLAEPLADPNNAEADPEA   LKLKSIIVSWAKKVL G
Signal peptide   Proregion   Matured peptide

Propeptide
Maturation process for MP-B
Figure 12-40. Molecular Biology of the Cell, 4th Edition.

Diagram illustrating the process of protein synthesis and secretion. Key components include:

- **mRNA** ( messenger RNA )
- **signal sequence**
- **cleaved signal peptide**
- **COOH plug**
- **NH2 plug**
- **ER LUMEN**
- **cytosol**

The process involves ribosomal subunits, mRNA binding, translation into polypeptide chains, and subsequent cleavage of signal peptides.

Additional annotations include: free ribosomal subunits, closed translocators, and the orientation of 5' and 3' ends of mRNA.
Structural comparison between mastoparan B and melittin

**Mastoparan B**

![Mastoparan B diagram]

**Melittin**

![Melittin diagram]
DPPIV: a drug target protein for Type II Diabetes

Review

Applications of dipeptidyl peptidase IV inhibitors in diabetes mellitus

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Abstract

A number of alternative therapies for type 2 diabetes are currently under development that take advantage of the actions of the incretin hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide on the pancreatic β-cell. One such approach is based on the inhibition of dipeptidyl peptidase IV (DP IV), the major enzyme responsible for degrading the incretins in vivo. DP IV exhibits characteristics that have allowed the development of specific inhibitors with proven efficacy in improving glucose tolerance in animal models of diabetes and type 2 human diabetics. While enhancement of insulin secretion, resulting from blockade of incretin degradation, has been proposed to be the major mode of inhibitor action, there is also evidence that inhibition of gastric emptying, reduction in glucagon secretion and important effects on β-cell differentiation, mitogenesis and survival, by the incretins and other DP IV-sensitive peptides, can potentially preserve β-cell mass, and improve insulin secretory function and glucose handling in diabetics.

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Keywords: Dipeptidyl peptidase IV; Glucose-dependent insulinotropic polypeptide; Glucagon-like peptide-1; Incretins; Diabetes mellitus
Proposed mechanism

Two Incretin:
- glucagon-like polypeptide-1 (GLP 1)
- glucose-dependent insulinotropic polypeptide (GIP)

N-terminal truncation

Inactive form
- DPPIV inactivates GIP in 5-7 min, and GLP-1 in 2 min

Active form

Taken from:
Structures of Some DPPIV inhibitors under animal or human testing

MK-0431 (Merck)
$IC_{50} = 18 \text{ nM}$

NVP DPP728 (Novartis)
$IC_{50} = 22 \text{ nM}$

Aminomethylpyridine (Roche)
$K_i = 0.1 \text{ nM}$

BMS-477118 (BMS)
$K_i = 0.45 \text{ nM}$

LAF237 (Novartis)
$IC_{50} = 3.5 \text{ nM}$
DPP-IV Structure

Taken from
PNAS 100, 5063 (2003)
Schematic structure for DDPIV
1. Propeller opening
2. Side opening

Taken from
Biochemical and Biophysical Research Communications 304, 73, (2003)
Schematic plot for active site

Taken from

Biochemical and Biophysical Research Communications 304, 73, (2003)
The Serine Proteases: Catalytic triad

Methodology

- Replica Exchange Method using Amber
- Docking simulation using Discover Studio
REM (Replica Exchange Method)

Very powerful method

- Each trajectory runs independently at different temperature.
- The trajectory (replica) is exchanged between the neighboring pairs with pre-determined interval.
- Linear computational scaling due to minimum communication loads between processors: suitable for the parallel machine.
  (very cheap nowadays)
Sampling coverage

Energy distribution

![Energy distribution graph with various temperatures](image)
comparison between the experimental (left) and simulated (right) structure of MP
Test of structural convergence

MP-C
Test of structural convergence

MP-C6
Test of structural convergence from different initial structures

Free energy landscape of MP-C in (RG, HB) space obtained from last 5 ns out of 360 ns simulation trajectory.

From helix structure

From linear structure
Test of structural convergence from different initial structures

Free energy landscape of MP-C6 in (RG, HB) space obtained from last 5 ns out of 360 ns simulation trajectory

From helix structure

From linear structure
Free energy landscape on (RG,RMSD) space for MP at 297 K
Binding affinity energy between the DDPIV and the first four residues of the promastoparans

<table>
<thead>
<tr>
<th>promastoparan</th>
<th>Binding energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMP-12</td>
<td>-6.616</td>
</tr>
<tr>
<td>PMP-10</td>
<td>-7.259</td>
</tr>
<tr>
<td>PMP-8</td>
<td>-8.548</td>
</tr>
<tr>
<td>PMP-6</td>
<td>-6.642</td>
</tr>
<tr>
<td>PMP-4</td>
<td>-7.292</td>
</tr>
<tr>
<td>PMP-2</td>
<td>-6.078</td>
</tr>
</tbody>
</table>
global energy-minimum structures of all the promastoparans.
free energy landscape on (RG, HB) space for prosequence of MP.

At 297K
Contents of secondary structure by DSSP analysis of prosequences

PMP-C12
Contents of secondary structure by DSSP analysis of prosequences

PMP-C10

![Graph showing population percentages of different secondary structures.](image-url)
Contents of secondary structure by DSSP analysis of prosequences

PMP-C8

![Graph showing the population of secondary structure elements across residue numbers. The graph includes lines for different secondary structures such as Helix, Bent, E-Strand, Trun, and Bridge, with population percentages on the y-axis and residue numbers on the x-axis.](image-url)
Contents of secondary structure by DSSP analysis of prosequences

PMP-C6

Population (%) vs. Residue Number

- Helix
- Bent
- E-Strand
- Trun
- Bridge
Contents of secondary structure by DSSP analysis of prosequences

PMP-C4

![Graph showing population distribution of secondary structures over residue number. The graph illustrates the percentage of residues in each secondary structure type (helix, bent, E-strand, turn, and bridge) across a range of residue numbers. The y-axis represents population percentage, and the x-axis represents residue number.]
Contents of secondary structure by DSSP analysis of prosequences
Overlapped view of docked promastoparans

The relative orientation is well preserved
The active site
The local structure of the binding site and with PMP docked inside.

The docking structure of the PMP-C12 while the pink arrow pointing the bond to be cleaved.
Overlap of the docking structures of all the promastoparans

dumb-bell shape represents the cleavage bond
2D projection plot of the inner surface of the pocket section in DPPIV

The location of the last non-hydrogen atom of the side chain for the first residue in a given promastoparan.
2D projection plot of the inner surface of the pocket section in DPPIV

The location of the last non-hydrogen atom of the side chain for the second residue in a given promastoparan
Conclusion

- The structural flexibility of DDPIV inhibitor comes from the pocket in DDPIV active site.
- The bond-breaking location is determined by the gate, which means the size of the inhibitors should be smaller 6.3 Å in height.
- The molecular ticketing process is controlled by the gate in DDPIV active site so is its endpoint.
- The structural design rules of DDPIV inhibitors can be derived from the structural restrictions of DDPIV active site.