Electronic Supplementary Information

Cholesterol-sensing role of phenylalanine in the interaction of human islet amyloid polypeptide with lipid bilayers

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Table S1 Secondary structure data of hIAPP and hIAPP_F15L in phosphate buffer at various time.

| Peptide       | Time (min) | Secondary structure (%) |
|---------------|------------|-------------------------|
|               |            | Helix | Strand | Turn | Unordere |
| hIAPP         | 0          | 16.7  | 26.9   | 25.6 | 30.8     |
|               | 60         | 20.3  | 25.2   | 24.7 | 29.7     |
|               | 150        | 5.7   | 31.7   | 26.4 | 36.2     |
| hIAPP_F15L    | 0          | 10.1  | 32.7   | 23.2 | 34.1     |
|               | 60         | 14.3  | 31.4   | 21.0 | 33.0     |
|               | 210        | 7.4   | 38.3   | 21.0 | 33.2     |
Fig. S3. CD spectra of hIAPP and hIAPP_{F15L} in phosphate buffer in the presence of DOPC, DOPC/20%Chol, DOPC/DPPC 1:2, DOPC/DPPC/Chol 1:2:1, DPPC and DPPC/20%Chol LUVs at various incubation time.
Table S2 Secondary structure data of hIAPP and hIAPP<sub>F15L</sub> in phosphate buffer in the presence of DOPC, DOPC/20%Chol, DOPC/DPPC 1:2, DOPC/DPPC/Chol 1:2:1, DPPC and DPPC/20%Chol LUVs at various incubation time.

| Peptide        | Lipid       | Time (min) | Secondary structure (%) |
|----------------|-------------|------------|-------------------------|
|                |             |            | Helix | Strand | Turn | Unordered |
| hIAPP          | DOPC        | 0          | 16.1  | 31.7   | 21.8 | 30.4       |
|                |             | 15         | 7.8   | 33.8   | 26.5 | 31.9       |
|                |             | 30         | 6.8   | 37.5   | 34.2 | 31.6       |
|                |             | 0          | 21.2  | 19.8   | 26.1 | 32.9       |
|                | DOPC/20%Chol| 60         | 23.2  | 22.9   | 21.8 | 32.2       |
|                |             | 120        | 17.4  | 29.9   | 21.0 | 31.7       |
| hIAPP<sub>F15L</sub> | DOPC        | 0          | 19.2  | 26.4   | 21.8 | 32.6       |
|                |             | 15         | 14.5  | 32.6   | 21.1 | 31.8       |
|                |             | 45         | 8.9   | 35.7   | 21.9 | 33.5       |
|                |             | 0          | 18.9  | 26.6   | 22.4 | 32.1       |
|                | DOPC/20%Chol| 90         | 15.3  | 24.5   | 24.3 | 35.8       |
|                |             | 135        | 7.8   | 33.2   | 29.2 | 29.9       |
| hIAPP          | DOPC/DPPC 1:2| 0          | 17.2  | 30.3   | 17.5 | 34.9       |
|                |             | 15         | 17.5  | 26.5   | 19.4 | 36.7       |
|                |             | 30         | 2.9   | 44.9   | 21.0 | 31.1       |
|                |             | 0          | 37.7  | 11.1   | 22.1 | 29.1       |
|                | DOPC/DPPC/Chol 1:2:1| 15       | 20.0  | 23.9   | 22.2 | 33.9       |
|                |             | 30         | 7.1   | 38.4   | 23.9 | 30.8       |
| hIAPP<sub>F15L</sub> | DOPC/DPPC 1:2| 0          | 7.3   | 36.7   | 22.0 | 34.2       |
|                |             | 15         | 4.8   | 41.4   | 21.9 | 31.9       |
|                |             | 45         | 4.5   | 40.2   | 21.4 | 33.9       |
|                |             | 0          | 7.6   | 33.3   | 24.9 | 34.3       |
|                | DOPC/DPPC/Chol 1:2:1| 45       | 7.1   | 30.3   | 24.9 | 37.6       |
|                |             | 90         | 4.1   | 41.4   | 21.5 | 33.0       |
| hIAPP          | DPPC        | 0          | 46.5  | 9.8    | 22.0 | 21.5       |
|                |             | 45         | 29.5  | 21.2   | 22.2 | 27.2       |
|                |             | 60         | 14.2  | 34.7   | 22.3 | 28.9       |
|                |             | 0          | 28.5  | 20.3   | 21.2 | 30.0       |
|                | DPPC/20%Chol| 30         | 17.2  | 31.1   | 21.0 | 30.6       |
|                |             | 60         | 14.2  | 34.7   | 22.3 | 28.9       |
| hIAPP<sub>F15L</sub> | DPPC        | 0          | 29.5  | 23.5   | 21.1 | 25.9       |
|                |             | 90         | 24.9  | 31.5   | 18.6 | 25.1       |
|                |             | 120        | 5.3   | 42.5   | 22.4 | 29.9       |
|                |             | 0          | 23.8  | 17.3   | 25.8 | 33.1       |
|                | DPPC/20%Chol| 90         | 11.3  | 28.8   | 23.4 | 36.5       |
|                |             | 105        | 8.6   | 36.9   | 25.5 | 29.1       |
**Fig. S4.** TEM images of hIAPP and hIAPP\textsubscript{1-19/F15L} measured after incubation in phosphate buffer for 30 min (A and B, respectively) and 5 h (C and D, respectively).

**Fig. S5.** $^1$H-NMR signals in the regions of 6.95-7.40 ppm (aromatic protons of F15 and H18-H\textsubscript{18}) and 3.96-4.03 ppm (V17-H\textsubscript{17}) used for calculation of dissociation constants of hIAPP\textsubscript{1-19} binding with DOPC (A) and DOPC/20\%Chol (B) LUVs. The $^1$H-NMR spectra were recorded in phosphate buffer at 25°C at various lipid-to-peptide ratios (L/P).
**Fig. S6.** $^1$H-NMR signals in the regions of 6.95-7.03 ppm (H18-H$_3$), 3.96-4.03 ppm (V17-H$_a$) and 2.97-3.02 ppm (K1-H$_6$) used for calculation of dissociation constants of hIAPP$_{1-19}$/F15L binding with DOPC (A) and DOPC/20%Chol (B) LUVs. The $^1$H-NMR spectra were recorded in phosphate buffer at 25°C at various lipid-to-peptide ratios (L/P).

**Fig. S7.** $^1$H-NMR signals in the regions of 6.95-7.40 ppm (aromatic protons of F15 and H18-H$_3$) and 3.96-4.03 ppm (V17-H$_a$) used for calculation of dissociation constants of hIAPP$_{1-19}$ binding with DPPC (A) and DPPC/20%Chol (B) LUVs. The $^1$H-NMR spectra were recorded in phosphate buffer at 25°C at various lipid-to-peptide ratios (L/P).
Fig. S8. ^1^H-NMR signals in the regions of 6.95-7.03 ppm (H18-H), 3.96-4.03 ppm (V17-H) and 2.97-3.02 ppm (K1-H) used for calculation of dissociation constants of hIAPP_{1-19/F15L} binding with DPPC (A) and DPPC/20%Chol (B) LUVs. The ^1^H-NMR spectra were recorded in phosphate buffer at 25°C at various lipid-to-peptide ratios (L/P).