Pharmacological Blocking of Interleukin-1ß Signaling Pathway Reduces Amyloid-Induced ß-Cell Toxicity in Human Islets

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BACKGROUND

- **Type 2 diabetes (T2D)** is characterized by peripheral insulin resistance, and progressive β-cell loss and dysfunction, leading to hyperglycemia.
- A key factor contributing to ß-cell death in T2D is islet amyloid deposition. **Islet amyloid** is formed by aggregation of β-cell hormone, human islet amyloid polypeptide (hIAPP). Amyloid also forms in cultured and transplanted human islets and contributes to islet graft failure in type 1 diabetes (T1D).

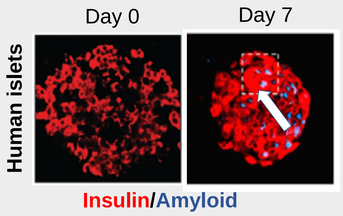

Fig 1: **:** Amyloid formation in human islets during culture

- **Islet inflammation** plays an important role in the pathogenesis of T2D. Islet amyloid formation triggers islet inflammation mainly by activation of the pro-inflammatory cytokine, interleukin-1β (IL-1β) signaling.

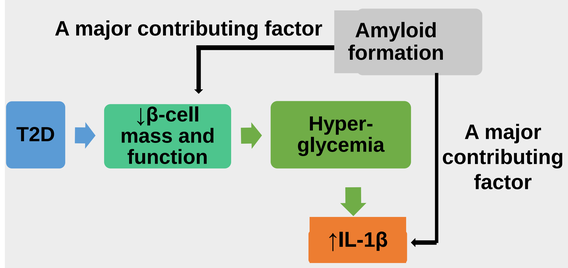

Fig 2. Amyloid formation is a major factor contributing to reduced β-cell mass and function leading to hyperglycemia and islet inflammation.

Treatments :

- **Anakinra** (Kineret) is an interleukin-1 receptor antagonist (IL-1RA) which prevents IL-1β signaling and IL-1β -induced islet inflammation.
- **Neutralizing antibody (nAb):** IL-1β neutralizing monoclonal antibody (nAb) blocks IL-1β signaling by targeting IL-1β.

HYPOTHESIS

We propose that treatment of human islets with anakinra and/or nAb may protect β-cells from amyloid toxicity by blocking amyloid-mediated activation of IL-1β signaling.

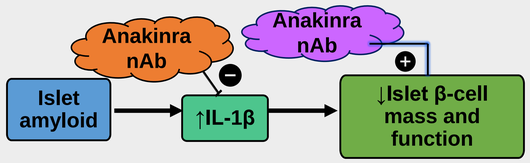

Fig 3: The mechanism of amyloid-induced β-cell toxicity and proposed protective effects of anakinra and nAb.

METHODS

- **Experimental model:** Human islets (n= 4 donors, purity >90%, assessed by dithizone staining)
- **Culture condition:** CMRL containing 11.1 mmol/l glucose (to form amyloid) for 7 days (37° C) without or with anakinra (10 µg/ml), nAb (1 µg/ml), or both.
- **Experimental method:** Quantitative immunostaining

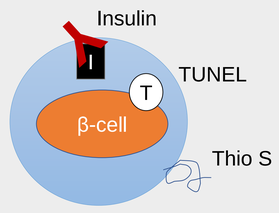

Fig 4: Paraffin imbedded human islet sections were immunolabelled for insulin, thioflavin S (amyloid) and TUNEL (apoptosis).

- **Statistics:** Statistical analyses were performed using one-way ANOVA (p<0.05 was taken as level of significance).

RESULTS

- Treatment with anakinra or nAb in human islets during 7-day culture reduced amyloid-induced β-cell apoptosis.

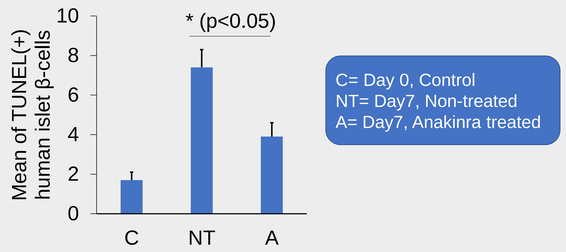

Fig 5. The proportion of TUNEL-positive (apoptotic) human islet β-cells after 7-day treatment with anakinra. Data are expressed as mean±SEM of three independent studies.

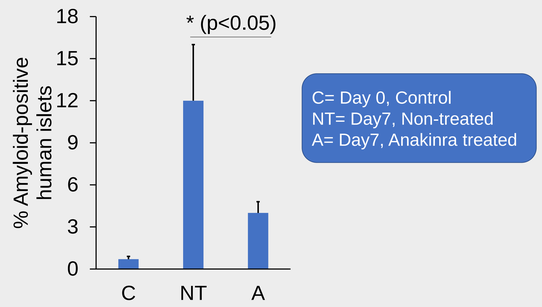

Fig 6. The proportion of amyloid-positive human islets with and without treatment with anakinra. Data are expressed as mean±SEM of three independent studies.

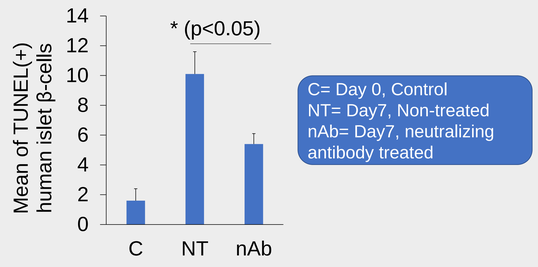

Fig 7. The proportion of TUNEL-positive (apoptotic) human islet β-cells before and after 7-days culture with or without nAb. Data are expressed as mean±SEM of three independent studies.

RESULTS, CONTINUED

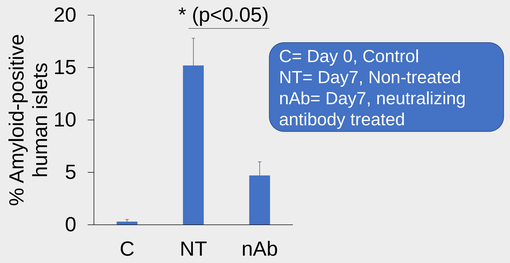

Fig 8. The proportion of amyloid-positive human islets in non-treated and nAb-treated groups. Data are expressed as mean±SEM of three independent studies.

CONCLUSION

- Treatment with anakinra or nAb markedly reduce amyloid formation and amyloid-induced β-cell death.
- Anakinra or nAb can protect human islet β-cells from apoptosis at least partially by reducing amyloid formation and blocking amyloid-mediated IL1-β signaling.
- Blocking IL-1β signaling may provide an effective therapeutic approach to protect β-cells from amyloid in T2D.

ACKNOWLEDGEMENTS

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