Modelling the Relationship Between Insulin Action and Insulin Clearance: Where Do We Have Saturation?

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Background and Aims

Developing the model structure for the insulin-glucose regulatory system with an intraperitoneal route of insulin delivery, we encountered questions regarding the relationship between insulin action and clearance:

Q1. Does the body clear all insulin after it has affected the glucose level?

Q2. Does the liver clear some insulin before it can affect the system?

Q3. What mechanisms cause saturation in insulin clearance?

Q4. Does the saturation also affect the insulin action?

Method

In pursuit of answers, we have comprehensively reviewed relevant physiology and mathematical modelling literature.

Results

Despite a shared receptor binding step between insulin action and clearance, the destiny of insulin after binding (Fig. 1c) diverges from the signal it dispatches to impact glucose level (Figs. 1a and 1b). Upon binding, insulin and receptors internalize into cells before undergoing degradation, with subsequent receptors recycling to the cell surface (Fig. 1c).

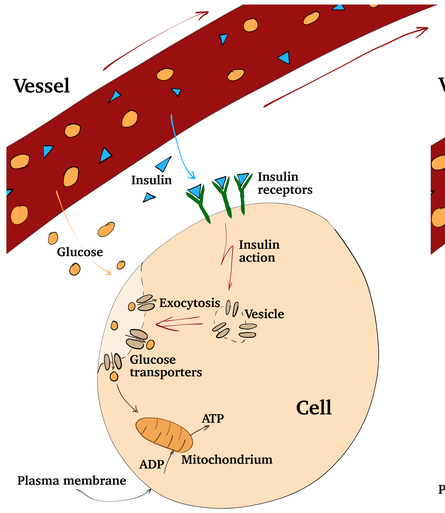

Fig 1a. Insulin action as an increase in GLUT4 transporters in the plasma membrane.

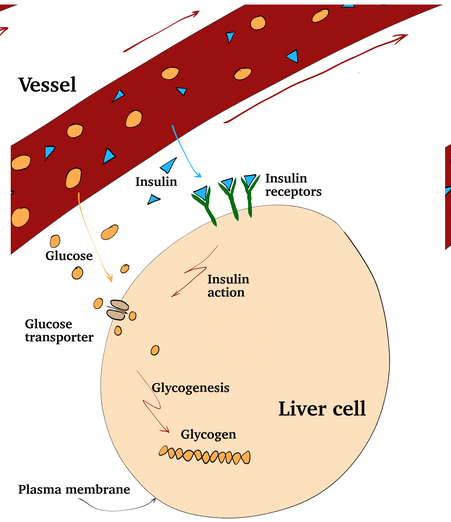

Fig 1b. Insulin action as an increased activity of glycogen synthesis

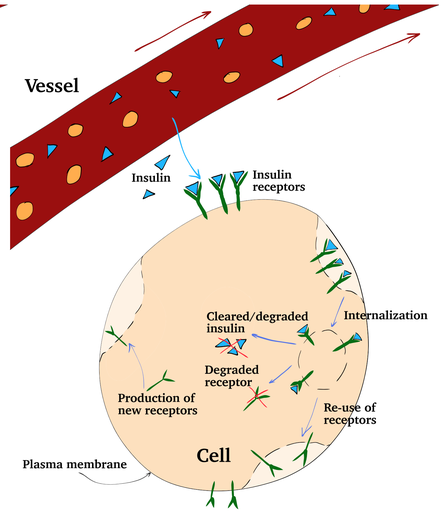

Fig 1c. Insulin clearance, as well as insulin receptor degradation, re-use and production, in a generic cell.

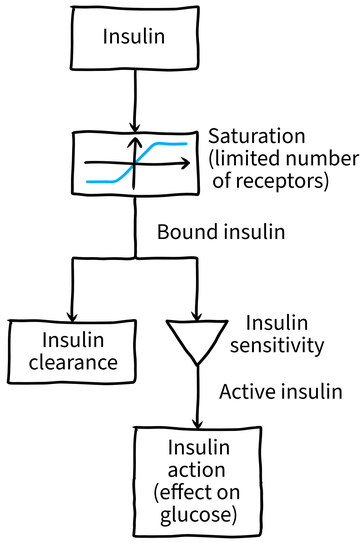

Fig 2a. Example of a *common* saturation function for insulin action and clearance (linear insulin clearance is not shown here). Used e.g., by Jamaludin (2013) and Benam (2023).

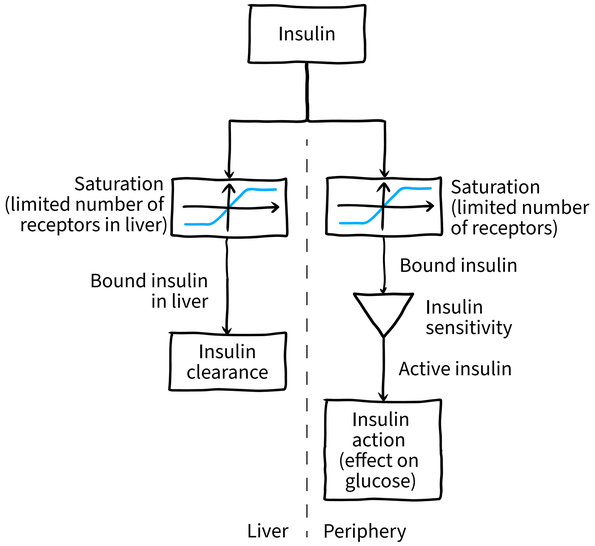

Fig 2b. Example of *separate* saturation functions for insulin action and clearance (linear insulin clearance is not shown here). Used e.g., by Dalla Man (2007).

Although some insulin may escape degradation after binding, the majority degrades (answer to Q1).

Insulin exerts its effects through a receptor triggered cascade of reactions. Given the receptor-based nature of insulin clearance (except in kidney), insulin likely exerts some effect on glucose before its clearance (answer to Q2).

Conclusion

The shared binding step suggests that saturation stemming from insufficient availability of receptors generally affects both insulin action and clearance (answers to Q3 and Q4). This should be taken into account when deciding about the model structure. Fig 2a and 2b show two different approaches for modeling saturation both in the insulin action and its clearance.

References

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- Jamaludin, U., *Developing and validating a new comprehensive glucose-insulin pharmacokinetics and pharmacodynamics model*, PhD Thesis, 2013.
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