Role of elevated airway glucose (and other biochemicals) in bacterial infections

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INTRODUCTION

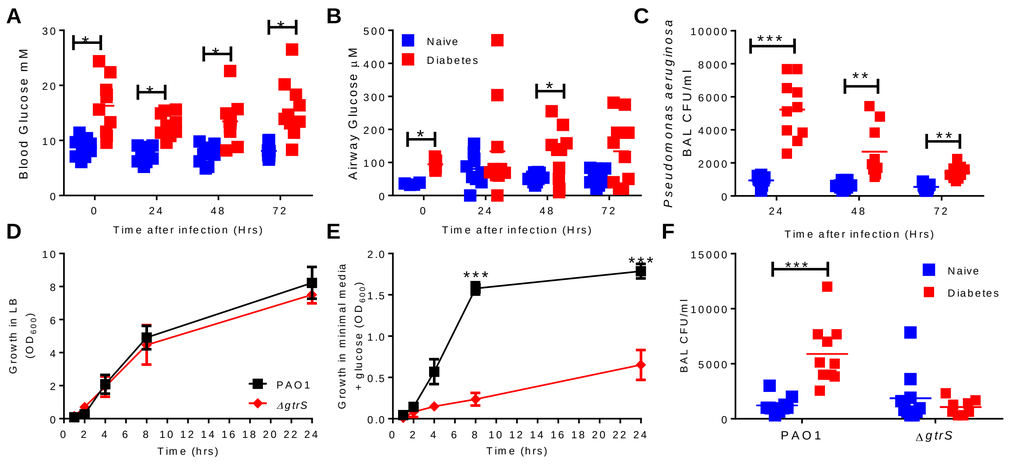
•Bacteria that live in the airways need something to eat: they mainly use host derived biochemicals, for example glucose.

•Regulation of airway biochemicals is a host mechanism to control infection.

•When levels of airway biochemicals are dysregulated, bacterial colonisation increases, enabling infection.

•We investigated how changes in airway glucose effect bacterial infection.

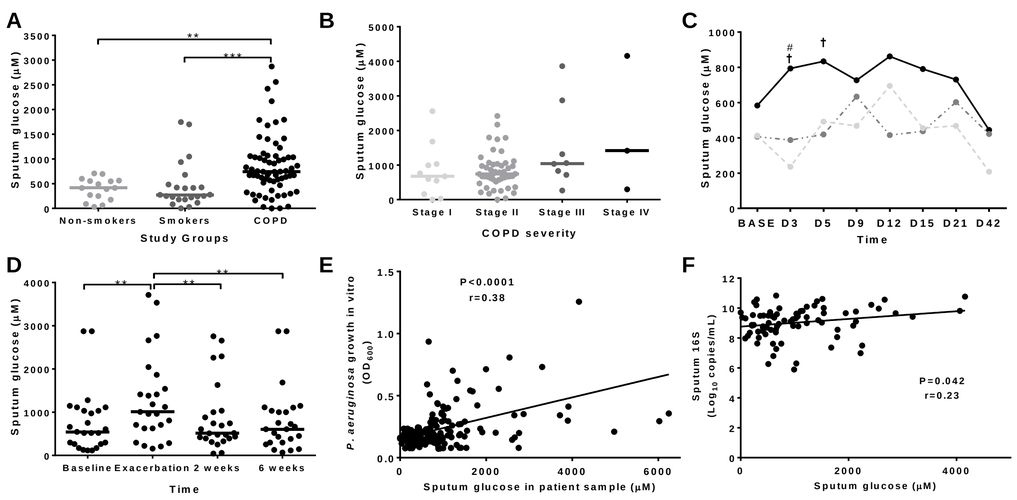
FIGURE 1: Hyperglycaemia in mice elevates airway glucose and bacterial load



Streptozocin induced diabetes increased both blood (A) and airway glucose (B) in mice. This was associated with a significant elevation in airway bacterial load after infection (C). To demonstrate that the increase in bacteria was driven by glucose, we generated *Pseudomonas aeruginosa* (strain PAO1) mutants in glucose uptake and metabolism genes (sensor kinase, Δ*gtrS* shown here), which grew normally on complete media (D), but were restricted in minimal media plus glucose (E). There was no significant increase in bacterial load in the airways in diabetic mice infected with knockout bacteria (F).

Data from Gill et al, Sci Reps 2016

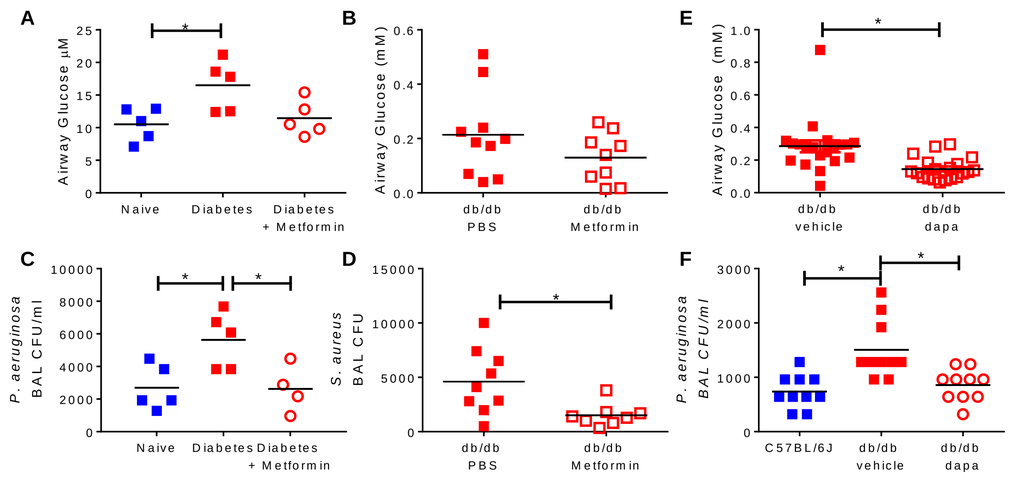
FIGURE 2: Airways glucose is elevated in COPD



Glucose levels in sputum were significantly higher in people with COPD than age matched smokers or non-smokers (A) and there was a trend towards increasing glucose with increasing COPD severity (B). Acute viral infection significantly increased airway glucose, after either volunteer rhinovirus challenge (C) or natural exacerbation (D). Sputum samples with greater levels of glucose supported more bacterial growth (E). Sputum glucose levels correlated with airway bacterial load measured by 16S rRNA gene PCR (F).

Data from Mallia et al, JACI 2018

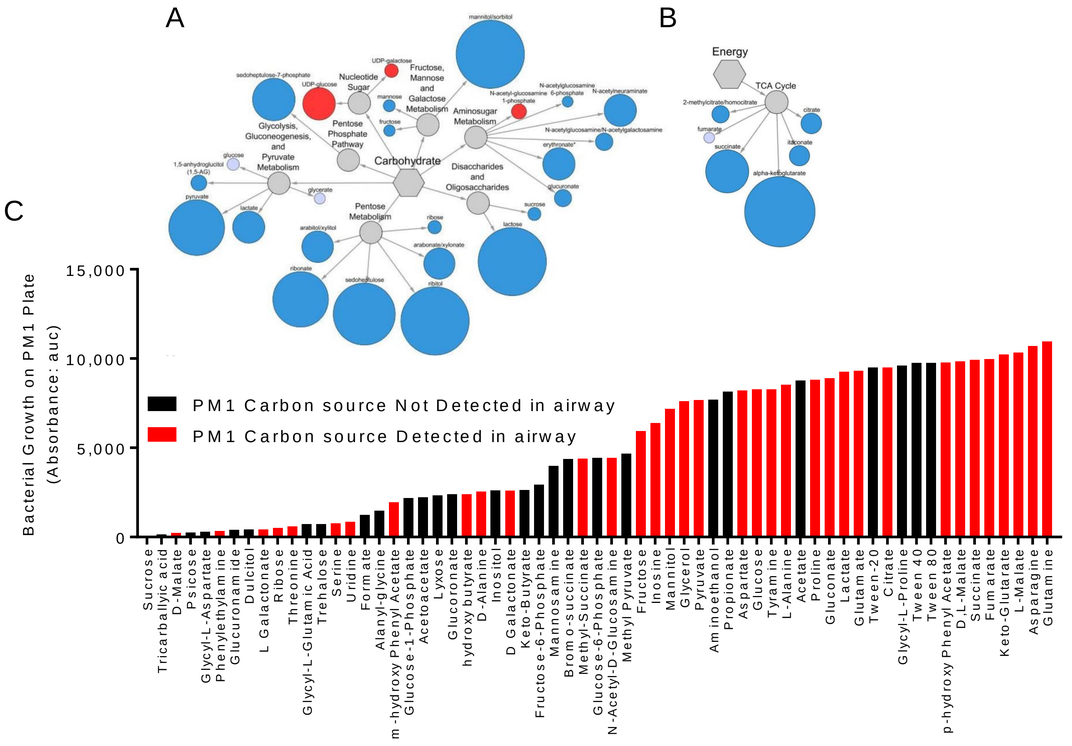
FIGURE 3: Treating with anti-diabetic drugs reduces airway glucose



Treating streptozocin induced diabetic mice (A) or obese diabetic mice (B) with metformin reduced airway glucose and significantly reduced airway P*. aeruginosa* (C) or *S. aureus* (D) infection. Treating obese diabetic (db/db) mice with dapafligitozon (E) reduced airway glucose and airway *P. aeruginosa* (F) after infection.

Data from Gill, Sci Reps 2016; Garnett, Thorax 2013; Astrand, BJP 2017.

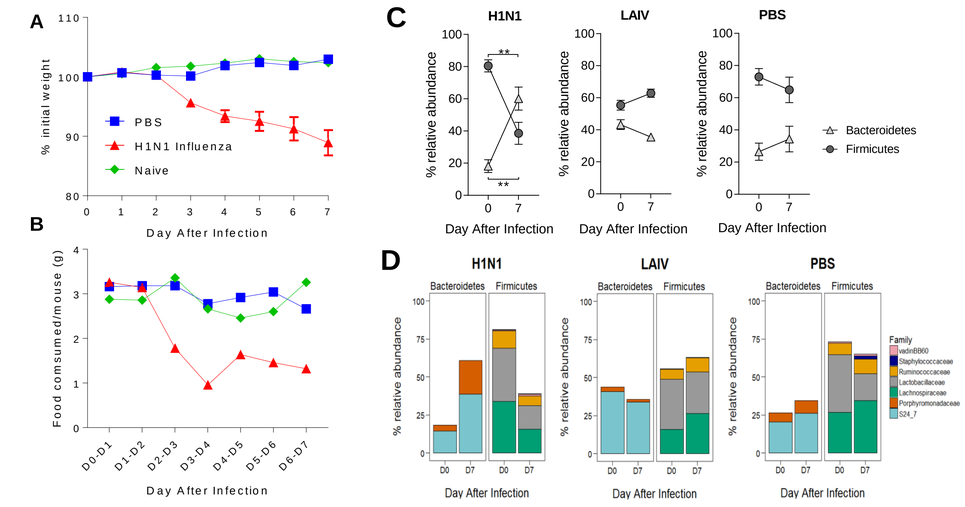
FIGURE 4: Glucose is one of several airway biochemicals that can support bacterial growth



Using a novel sampling method, we recovered samples from the upper and lower airways. They were analysed for biochemical composition by mass spectrometry. 581 biochemicals were found in the airways. A number of airways that were in the carbohydrate (A) or energy (B) super families were tested for whether they supported *P. aeruginosa* growth (C).

Data from Farne et al, in revision

FIGURE 5: Altering the biochemical balance alters microbial composition

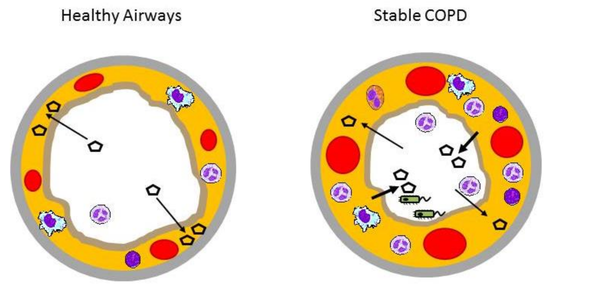


Infection with H1N1 influenza led to weight loss in mice (A) and this was associated with a significant reduction in food intake (B). Infection induced anorexia led to a significant change in gut microbiota, with an increase in Bacteroidetes and decrease in Firmicutes (C). Significant changes were also seen at the family level, though the relative abundance of specific families varied across experimental repeats suggesting it is a broad change in environment (D)

Data from Groves et al, Frontiers in Immunology 2018

Conclusion and future work

- Bacterial growth in the airways is supported by the biochemicals in the airways.
- Inflamed airways in patients with COPD may be enriched for biochemicals that support growth, leading to greater colonisation and infection.
- Reducing biochemical availability represents a new anti-bacterial strategy.
- We aim to investigate the effect of metformin on airway glucose in COPD.



REFERENCES

Gill SK, Hui K, Farne H, Garnett JP, Baines DL, Moore LS, Holmes AH, Filloux A, J.S. Tregoning+. 2016. Increased airway glucose increases airway bacterial load in hyperglycaemia. Sci Rep.

P. Mallia, J.Webber, S.K. Gill, M.Trujillo-Torralbo, M.A. Calderazzo, L. Finney, E. Bakhsoliani, H. Farne, A. Singanayagam, J. Footitt, R. Hewitt, T. Kebadze, J. Aniscenko, V. Padmanaban, P.L. Molyneaux, I.M. Adcock, P.J. Barnes, K. Ito, S.L. Elkin, O.M. Kon, W.O. Cookson, M.F. Moffat, S.L. Johnston*, J.S. Tregoning*,+. 2017. Role of airway glucose in bacterial infections in Chronic Obstructive Pulmonary Disease. JACI.

Garnett, J.P., E.H. Baker, S. Naik, J.A. Lindsay, G.M. Knight, J.S. Tregoning and D.L. Baines. 2013. Metformin reduces airway glucose permeability & hyperglycaemia-induced Staphylococcus aureus growth. Thorax.

Åstrand A, Wingren C, Benjamin A, J.S. Tregoning, Garnett JP, Groves H, Gill S, Orogo-Wenn M, Lundqvist AJ, Walters D, Smith DM, Taylor JD, Baker EH, Baines DL. 2017. Dapagliflozin-lowered blood glucose reduces respiratory P. aeruginosa infection in diabetic mice. British Journal of Pharmacology.

H. Farne, H.T. Groves, S.K. Gill, I. Stokes, M. Trujillo-Torralbo, S.L. Johnston, P. Mallia, J.S. Tregoning. Comparative metabolomic sampling of upper and lower airways by different methods demonstrates that synthetic absorptive matrix strips recover the most biochemicals. *In revision*.

H.T. Groves, L. Cuthbertson, P. James, M. Moffatt, M. Cox*,+, J.S. Tregoning*,+.2018. Respiratory disease following viral lung infection alters the murine gut microbiota. Frontiers in Immunology.