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We are grateful to Fehsel & Löffler for their response which provides a thought-provoking summary of the possible role of Protein Kinase B (Akt) in predisposing those with first-episode psychosis (FEP) to dysglycaemia, which they consider a potential explanation for the findings of our meta-analysis (1). We found that markers of prediabetes were more common in those with FEP than in healthy matched controls. As they rightly state, we were unable to show causality in our findings, which were observational. However, we did present our own possible explanation; that the two disorders may share intrinsic inflammatory disease links.

Whilst their explanation appears different to our own, it may not be entirely distinct. Increased dopamine D2 receptor blockade, a crucial aspect of the pathophysiology of schizophrenia, causes inhibition of Akt phosphorylation and therefore the glycogen synthase kinase 3 (Gsk-3) pathway (2). Previous findings have demonstrated that glycogen synthase kinase-3 is an important regulator of both the innate and adaptive immune systems' contributions to inflammation (3).

Studies of the innate immune system have shown that inhibitors of GSK3 profoundly alter the inflammatory response of both peripheral and central cells. GSK-3 has been shown to upregulate expression of the inflammatory transcription factor NF- κ B (3), which has previously been linked to schizophrenia (4).

Furthermore, GSK3 reduces the production of the anti-inflammatory cytokine IL-10 (3), and inhibitors of GSK3 increased anti-inflammatory cytokine production. Work on antipsychotic naïve FEP patients has shown decreased levels of IL-10 in comparison to healthy controls, with levels of IL-10 inversely proportional to negative symptomatology (5).

Therefore, the GSK-3/Akt pathway might be an important contributor to the hypothesis of shared inflammatory disease links between dysglycaemia and psychosis. Future work might investigate the cytokines implicated in the GSK-3/Akt pathway alongside dysglycaemia, in those with first-episode psychosis to further elucidate the link between the two conditions.

References

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