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Dopaminergic pathways in obesity-associated immuno-metabolic depression

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Immuno-metabolic diseases emerge in clusters since a state of chronic systemic inflammation associated to metabolic dysfunction disrupts homeostasis in multiple organs such as adipose tissue and brain (Hotamisligil, 2017). The association between obesity and depression is well established (Lasselin and Capuron, 2014), although the underlying pathophysiological mechanisms remain unrevealed. Lamers *et al.* (2018) found increased appetite as the core symptom driving the associations between depression and both metabolic and inflammatory markers highlighting a specific biological type of depression. The novelty of such findings resides in the mechanisms regulating appetite such as dopaminergic pathways being also involved in immunomodulation and inflammation. Systemic inflammation is a stronger contributor of obesity-related depressive symptoms than metabolic dysfunction *per se* (Delgado *et al.*, 2018). Major depressive disorder patients, during a depressive episode, have a subclinical inflammation and reduced response to lipopolysaccharide in monocytes (Zhang *et al.*, 2018). Moreover, higher leptin was associated with hyperphagia, independently from weight (Milaneschi *et al.*, 2017). We found that plasma levels of leptin, very-low-density lipoprotein-cholesterol and CD14 expression in monocyte subsets are predictors of subclinical inflammatory obesity (Leite *et al.*, 2017*a*), which can constitute an important tool for early therapeutic interventions in obesity-related comorbidities, namely depression.

Dopaminergic pathways have a major role in appetite regulation and as immunoregulators in inflammation. Immune cells, neurons and adipocytes share common signalling pathways mediated by catecholamines (CA), and dopamine (DA) plays a prominent and so far, possibly underestimated role (Flierl *et al.*, 2008; Borcherding *et al.*, 2011; Pinoli *et al.*, 2017). DA regulates behaviour, reward, movement, endocrine, cardiovascular, renal and gastrointestinal functions, but it is also a crucial transmitter in the neuroimmune network, contributing to the nervous–immune systems interplay as well as in the communication among immune cells (Pinoli *et al.*, 2017). We showed that central obesity is associated with a distinct pattern of CA receptors in circulating immune cells and that β_2-adrenoceptors (AR) and dopaminergic receptors (DR)D_2 might be protective towards visceral obesity (Leite *et al.*, 2016, 2017*b*). β_2-AR and DRD_2 transcripts were associated with lower inflammatory pattern of monocytes and with a better metabolic profile, suggesting an immunomodulatory role for CA in obesity-associated inflammation.

DA exerts its effects through the interaction with five different DR (D_{1-5}). Human monocytes express all DR and evidence suggests that DA inhibit monocyte NLRP3 inflammasome thus resulting in the reduction of the inflammatory processes (Pinoli *et al.*, 2017).

Monocytes in peripheral blood are considered as classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$) and non-classical monocytes ($CD14^{+}CD16^{++}$). Expansion of the intermediate monocyte subset has been described in chronic inflammatory diseases (Wong *et al.*, 2012), while the contribution of non-classical monocyte subset in inflammation remains unclear.

We studied DR expression in human monocyte subsets and the effect of DA on phosphorylation of monocyte signal transducer and activator of transcription 3 (STAT3), a crucial step in the production of pro-inflammatory cytokines in obesity and interacts with the double-stranded RNA-sensing kinase PKR, a critical mediator of inflammasome activity and metabolic regulation (Hotamisligil, 2017). Our results show that all five DR are expressed by circulating monocytes, however DR+ cells are on average only 16–33% of classical and intermediate monocytes but about 89–96% of non-classical monocytes, and incubation of whole blood with DA reduced IL-6-induced phosphorylation of STAT3 in CD14+ monocytes (Fig. 1).

Preferential DR expression on non-classical monocytes in comparison with classical and intermediate monocyte subsets suggests that DA anti-inflammatory effects involve mainly non-classical monocytes. Our findings in human monocytes of reduction of IL-6-induced

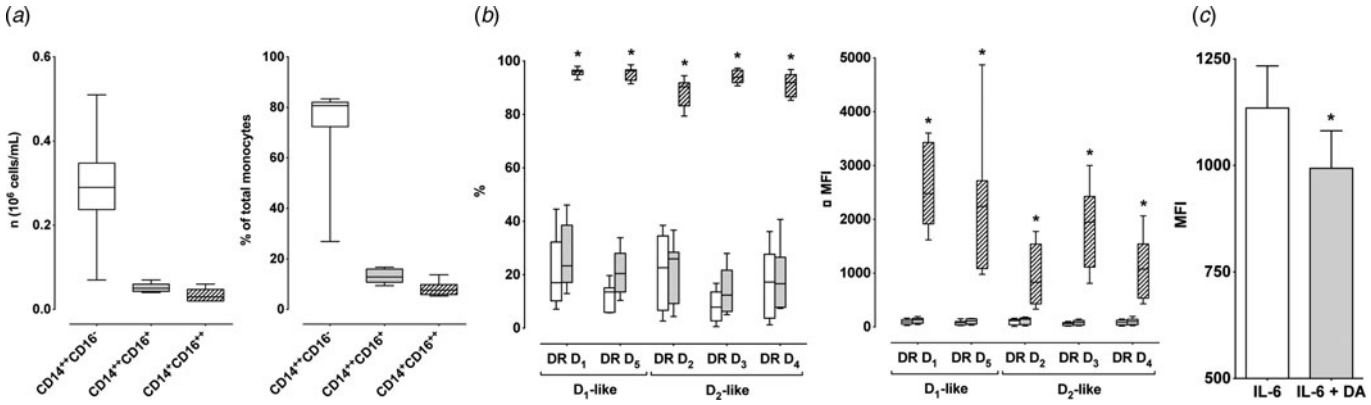

Fig. 1. Dopaminergic receptors are preferentially expressed on proinflammatory monocytes and dopamine downregulates STAT3 phosphorylation. (*a*) In peripheral blood, the majority of circulating monocytes is represented by classical (CD14++ CD16−) monocytes, while intermediate (CD14++ CD16+) and proinflammatory (CD14+ CD16++) monocytes are on average, respectively, 13% and 8% of total monocytes. (*b*) Both D1- and D2-like dopaminergic receptors (DR) are expressed by circulating monocytes; however, while on average only 16–33% of classical (empty) and intermediate (shaded) monocytes are DR+, with low expression levels, about 89–96% of proinflammatory monocytes (dashed) are DR+, with high expression levels. (*c*) Incubation of whole blood with dopamine 1 μM reduces IL-6 100 ng/mL-induced phosphorylation of STAT3 in CD14+monocytes (methodology in online Supplementary Information).

STAT3 phosphorylation by DA infers an immunomodulatory role for this CA given STAT3 function in the production of pro-inflammatory cytokines and its interaction with PKR mediating metabolic signals and inflammasome activity.

DA and dopaminergic agonists interfere with tumour necrosis factor-α and nitric oxide production in mouse monocytes and DA modulate the expression of surface markers, such as the Fc-γ receptor, important for host defence (Pinoli *et al.*, 2017). This suggests that dopaminergic pathways in human monocytes may counteract the effects of proinflammatory stimuli, acting on the non-classical subset and to a minor extent in the intermediate subset, the main responding subset of monocytes to standardized low-grade inflammation (Thaler *et al.*, 2016).

Macrophages convey information to the nervous system regulating behaviour, metabolism and inflammation through direct access to CA produced by the sympathetic nerve (Camell *et al.*, 2017). However, monocytes/macrophages themselves produce CA (Marino and Cosentino, 2013; Pinoli *et al.*, 2017). CA, particularly DA, are key signalling molecules connecting monocytes/macrophages, adipocytes and sympathetic nerve terminals thus regulating immuno-metabolic disease clusters including depression. Dopaminergic pathways might thus allow simultaneously targeting adiposity, inflammation and the immuno-metabolic depression.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718001587.

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