OC30: Diabetic rats lose A2A receptor-mediated facilitation of ileal myenteric cholinergic neurotransmission

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Introduction: Enteric dysmotility is a long-term complication of Diabetes mellitus that causes significant discomfort in 76% of diabetic outpatients [1].

Objective: Knowing that purines may be involved in synaptic transmission modifications in the CNS of diabetic rats [2], we decided to investigate if purinergic dysfunction could also play a role in diabetic enteric neuropathy in rats.

Material and Methods: Adult male Wistar rats injected with streptozotocin (STZ-rats, 55mg/kg, IP) became hyperglycemic (412±10 md/dL, n=48) in 48 hours. Experiments were performed at day 14 on longitudinal muscle-myenteric plexus (LM-MP) of the ileum of control and STZ-rats. By HPLC analysis, we showed that extracellular ATP (30 µM) hydrolysis is faster (t½ 4.3±0.5 min, n=3) in STZ-rats than in control animals (t½ 7±1 min, *n*=6). Despite the faster adenosine formation from ATP in STZ-animals, the nucleoside hardly accumulates in the LM-MP because adenosine (30 µM) was inactivated into inosine more rapidly in STZ-rats (t½ 13±3 min, n=4) than in control animals (t½ 34±1, n=4) [2]. The inhibitory effect of the A_1 receptor agonist (R-PIA, 300 nM) on evoked [^{3}H]-acetylcholine ([^{3}H]-ACh, 5 Hz, 200 pulses of 1ms) was similar in control (-36±4%, n=4) and STZ (-45±8%,n=3) rats. Conversely, the A_{2A} receptor agonist, CGS 21680C (3nM), facilitated [^{3}H]-ACh release by 53±10% (*n*=4) in control animals but not in diabetics (-19±7%, n=3). Confocal microscopy studies indicate that immunoreactivity against A_1 receptors in maintained, but A_{2A} labeling decreases in STZ-rats.

Conclusion: Though adenosine formation is faster in the LM-MP of diabetic rats the nucleoside is rapidly inactivated. Low extracellular adenosine levels, together with the functional loss of A_{2A}-receptor-mediated facilitation of cholinergic neurotransmission may contribute to constipation, the most common GI complaint of diabetic patients.

Acknowledgments: FCT (PEst-OE/SAU/UI0215/2014).

References

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