ABSTRAK

Latar Belakang: Komplikasi tractus digestivus dapat terjadi pada perjalanan penyakit diabetes. Komplikasi tersebut antara lain diperantarai oleh kematian neuron plexus myentericus colon. Sitokin inflamasi TNF-α dilaporkan meningkat pada tikus diabetes. Penelitian ini bertujuan untuk mengetahui jalur kematian neuron, korelasi jumlah neuron plexus myentericus dengan gangguan fungsional colon dan peran penghambatan sinyal TNF-α pada kematian neuron plexus myentericus colon tikus diabetes.

Metode: Tiga puluh ekor tikus dibagi menjadi 3 kelompok yaitu kontrol normal (KN), kontrol diabetes (KD), dan diabetes yang mendapat antagonis TNF-α, etanercept (DE). Diabetes diinduksi dengan menggunakan streptozotocin dan nicotinamide. Etanercept diberikan 2 kali seminggu pada tikus kelompok DE. Kadar glukosa darah puasa tikus diperiksa 2 minggu sekali dan berat badan diukur setiap minggu. Waktu transit colon, karakteristik feses dan kadar TNF-α plasma diperiksa pada akhir penelitian (minggu ke-10). Setelah tikus dikorbankan, colon diambil dan diukur berat serta panjangnya. Jaringan colon digunakan untuk memeriksa jumlah neuron dengan metode disektor, kadar TNF-α serta ekspresi protein RAGE, TNF-α, TNFR1, gasdermin D, caspase-3 aktif dan MLKL terfosforilasi. Jumlah neuron dikorelasikan dengan fungsi colon.

Hasil: Pemberian antagonis TNF-α tidak mampu menurunkan kadar glukosa darah dan tidak memperbaiki berat badan, gangguan fungsional dan jumlah neuron plexus myentericus colon tikus diabetes. Jumlah neuron berkorelasi positif dengan waktu transit colon. Colon DE lebih pendek dan lebih ringan dibanding KD menunjukkan etanercept mencegah pembesaran colon. Ekspresi RAGE, TNF-α, gasdermin D dan caspase-3 aktif pada plexus myentericus tikus DE lebih lemah dibanding KD, ekspresi MLKL terfosforilasi tikus DE tidak berbeda dengan KD namun lebih kuat dari KN, ekspresi TNFR1 tidak berbeda pada ketiga kelompok perlakuan.

Kesimpulan: Jalur apoptosis, pyroptosis dan necroptosis teraktifkan pada plexus myentericus. Jumlah neuron berkorelasi positif dengan waktu transit colon. Penghambatan sinyal TNF-α tidak mencegah kematian neuron namun mencegah pembesaran colon tikus diabetes.

Kata kunci: Diabetes; kematian neuron plexus myentericus; sinyal TNF-α

ABSTRACT

Background: Digestive tract complications can occur in diabetes**.** It may be mediated by neuronal death in the myenteric plexus of the colon. Increased proinflammatory cytokine tumor necrosis factor (TNF)-α was reported in diabetic rats. The study aimed to investigate neuronal death pathway, correlation between neuron number with colonic dysfunction and role of TNF-α signaling inhibition on neuronal death in myenteric plexus of colon in diabetic rats.

Methods: Thirty rats were divided into normal control (NC), diabetic control (DC), and diabetic with TNF-α antagonist, etanercept (DE) groups. Diabetes was established by streptozotocin and nicotinamide. The DE group was injected with etanercept twice a week. Blood glucose level was measured every 2 weeks and body weight was measured weekly. In the end of study (week 10), fecal pellet, colonic transit time, and plasma TNF-α were measured. Colon was dissected out, followed by weight and length measurements. Colonic tissue used to measure neurons number, TNF-α level and expression of RAGE, TNF-α, TNFR1, gasdermin D, activated caspase-3, phosphorylated MLKL. Neuron number was correlated with colonic function.

Results: TNF-α antagonist administration had no effect on blood glucose, body weight, colonic function and neuron number in myenteric plexus of diabetic groups. Neuron number correlated positively with colonic transit time. The DE had a shorter and lighter colon than the DC. It showed that etanercept had an effect on colon enlargement prevention. Weaker immunoreactivity of RAGE, TNF-α, gasdermin D and activated caspase-3 observed in the myenteric plexus of DE rat's colon compared to the DC group. Immunoreactivity of phosphorylated MLKL of the DE comparable with the DC, but stronger than NC, and TNFR1 immunoreactivity were not different in all groups.

Conclusions: Apoptosis, pyroptosis and necroptosis pathways are activated in myenteric plexus. Neuron number correlated with colonic transit time. TNF-α signaling inhibition does not prevent neuronal death but prevents colon enlargement in diabetic rats.

Keywords: Diabetes; neuronal death in myenteric plexus; TNF-α signal