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Investigating intestinal smooth muscle dysfunction in the 6-OHDA rat model of Parkinson's disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, den 15 juni 2022, klockan 13:00

av
Maria del Pilar Murillo Angarita

Fakultetsopponent:
Scott Smid, PhD
The University of Adelaide, Australia

Avhandlingen baseras på följande delarbeten

I. **Murillo, M.D.P.**, Aronsson, P., Winder, M., Carlsson, T. *Desipramine, commonly used as a noradrenergic neuroprotectant in 6-OHDA-lesions, leads to local functional changes in the urinary bladder and gastrointestinal tract in healthy rats.* **Heliyon.** 6: e05472.

II. **Murillo, M.D.P.**, Johansson, E., Bryntesson, V., Aronsson, P., Tobin, G., Winder, M., Carlsson, T. *Alterations in smooth muscle function of colonic segments in the 6-hydroxydopamine rat model of Parkinson's disease.*
Manuscript submitted

III. **Murillo, M.D.P.**, Aronsson, P., Tobin, G., Winder, M, Carlsson, T. *Monoaminergic smooth muscle responses in colonic and ileal segments in the 6-hydroxydopamine rat model of Parkinson's disease.*
Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Investigating intestinal smooth muscle dysfunction in the 6-OHDA rat model of Parkinson's disease

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Abstract

The neurodegenerative progression of the nigrostriatal pathway in Parkinson's disease (PD) entails the appearance of motor and nonmotor symptoms. Nonmotor symptoms are common, having a negative impact on the quality of life of patients living with PD. Among these symptoms, autonomic dysfunction is particularly bothersome affecting the intestinal function. This thesis explores the role of the smooth muscle in the impaired enteric neurotransmission seen in PD using the 6-OHDA rat model, a well-standardized and validated model of PD.

A *priori* experimental revision of the model demonstrated that a commonly used neuroprotective drug in 6-OHDA rat stereotaxic surgery, desipramine, interferes with the peripheral assessment of urinary bladder and intestinal motility. Therefore, it was omitted to minimize confounding factors when studying peripheral autonomic dysfunction.

Ileal and colonic dysfunction was assessed by electrical field-, cholinergic, and monoaminergic stimulation in smooth muscle strips and/or segments. Colonic enhancement of electrically-induced and cholinergic-evoked contractile responses was found, correlating with previously described upregulation of muscarinic receptors. Moreover, this cholinergic impairment shown to be related to altered inhibitory signaling. In addition, serotonergic neuromodulation displayed alterations in both colon and ileum following central dopamine lesion. Catecholaminergic-induced intestinal motility, however, showed no differences despite previous studies identifying a reduction of dopaminergic and noradrenergic neurotransmission. These findings increase the understanding of complex interactions between enteric neurotransmitters after central dopamine neurodegeneration affecting the intestinal function and may contribute in the future to discover novel therapeutic approaches based on these interactions.

Keywords: Intestinal motility, smooth muscle, enteric nervous system, dopamine neurodegeneration

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