

## **BUTYRATE ATTENUATES MOTOR DEFICITS AND ANTIBIOTIC-INDUCED INTESTINAL DAMAGE IN 6-HYDROXYDOPAMINE MODEL OF PARKINSON'S DISEASE IN MICE**

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A link between gut microbiota composition and Parkinson's disease (PD) has been recently recognized. Indeed, gastrointestinal dysfunction often precedes motor symptoms, suggestive of the onset of PD (Sampson et al., 2016). Actually, it has also been demonstrated that PD patients showed an altered gut microbiota, probably caused by an increased intestinal permeability, due to a reduction in tight junction protein expression. All these findings are clearly consistent with an increased capacity of gut-microbiota-derived products, such as lipopolysaccharide and other neurotoxins, to reach the bloodstream and induce a systemic inflammation occurring in PD patients.

Gut microbiota alteration in PD patients has been associated to a reduction in those bacteria producing short chain fatty acids (SCFAs) (Unger et al., 2016). Therefore, the shift in gut microbiota associated to PD could be related to a shift in metabolite production, underlying gastrointestinal and motor dysmotility in PD.

Among all SCFAs, butyrate is the most potent inhibitor of histone deacetylase (HDACi), whose activity finely regulates the transcription of genes involved in neuronal cell homeostasis. Since PD, as many brain disorders, is associated with imbalance in protein acetylation and transcription dysfunction, HDACi, and in particular butyrate, have demonstrated to be of therapeutic potential in epigenetic treatment of neurodegenerative diseases.

Our aim was to analyze whether dysbiosis could worsen PD symptoms and whether sodium butyrate (BuNa), through an epigenetic mechanism, could be able to affect gastrointestinal dysfunction in PD or PD neurodegenerative process itself and try to discriminate between its central and/or peripheral effect.

In order to induce gut microbiota dysbiosis, mice were treated with ceftriaxone (8g/kg, per os) for 5 days, as already reported (Ling et al., 2015); afterwards mice were unilaterally injected with 6-hydroxydopamine (6-OHDA, 4 µg/2 µl) in the right striatum (Avagliano et al., 2016). To evaluate butyrate effect on Parkinson symptoms, mice were treated with butyrate (100 mg/kg os) once daily for 14 days, starting the day when mice were challenged with neurotoxin injection.

Therefore, mice were divided into several experimental groups: 1) CTR, control mice receiving intrastriatal injection of vehicle; 2) CFX, mice receiving the antibiotic for 5 days; 3) 6-OHDA, mice challenged with 6-OHDA; 4) CFX+6-OHDA, mice receiving CFX for 5 days and 6-OHDA injection, 5) 6-OHDA+ BuNa, mice challenged with 6-OHDA and treated with BuNa; 6) CFX+6-OHDA+BuNa, mice receiving CFX, 6-OHDA intrastriatal injection and BuNa treatment.

At day 3, 7 and 14 post-6-OHDA injection, behavioral tests (rotarod and apomorphine test) were assessed in all groups. Then oxidative stress and inflammatory markers were measured in striatal and colonic homogenate 14 days after BuNa treatment.

We observed that treatment with BuNa attenuated motor deficits, oxidative stress and neuroinflammatory markers. In particular, in the rotarod test, the time spent on the rotating rod was significantly decreased after 3, 7 and 14 days in the 6-OHDA group when compared with the control group, but this performance was worsened in intestinal-injured animals. BuNa administration significantly prevented motor impairment at all experimental time considered versus 6-OHDA and CFX+6-OHDA. Total rotations induced by the apomorphine in the CFX+6-OHDA group were significantly increased as compared to 6-OHDA group at 3, 7 and 14 days. BuNa treatment ameliorated 6-OHDA-induced neurobehavioral deficit as early as within 3 days of treatment and effects were even more marked and significant after 7 and 14 days of treatment.

These findings reveal that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiota represent a risk factor for PD.

Avagliano et al. (2016). *Pharmacol Res.* 113(Pt A):276-289.

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