Press release: European College of Neuropsychopharmacology (ECNP) Congress, Copenhagen

Scientists find psychiatric drugs affect gut contents

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Type of study: Peer reviewed/experimental work/animals

Scientists have found that antidepressants and other psychiatric drugs can change the quantity and composition of gut bacteria in rats. These results raise questions about the specificity of psychoactive drug action, and if confirmed in humans whether psychiatrists might need to consider the effects on the body before prescribing. The research team is currently carrying out a large-scale human observational study which aims to answer the questions posed by these findings. This work is presented at the ECNP Conference in Copenhagen following part-publication in a peer-review journal (see Notes for Editors).

Scientists are increasingly finding that the *microbiome* – the bacterial content of the digestive system – has effects on other functions in the body, and vice versa. A group of Irish-based scientists has given 7 groups of rats (8 animals in each group) normal or slightly elevated levels of individual psychopharmaceuticals, including Lithium, valproate, and the antidepressants fluoxetine (Prozac) and escitalopram. After 4 weeks of treatment, the scientists examined the gut bacteria – the microbiome – to see what the effects the drugs had (see abstract for experimental details).

They found that some drugs consistently increased the number of certain bacteria in the gut. For example, lithium and valproate (both used for bipolar disorder) increased the numbers of *Clostridium* and other bacteria. In contrast, the (SSRI) antidepressants escitalopram and fluoxetine significantly inhibited growth of bacterial isolated strains such as *E.coli*.

Describing the work, lead researcher, Ms Sofia Cussotto (University College, Cork) said:

"We found that certain drugs, including the mood stabiliser lithium and the antidepressant fluoxetine, influenced the composition and richness of the gut microbiota. Although some psychotropic drugs have been previously investigated in in vitro settings, this is the first evidence in an animal model.

There are several implications of this work. First of all, some studies have shown that depressed or schizophrenic patients can have altered microbiota composition, therefore psychotropic drugs might work on intestinal microbes as part of their mechanisms of action. Of course, this has to be proved. Given that antidepressants, for example work on some people but not others, making an allowance for microbiome may change an individual's response to antidepressants. On the other hand, microbiome-targeting effects might be responsible for the side effects associated with these medications. All these hypotheses have to be tested in preclinical models and in humans, and this is our next step".

Commenting, Professor Serguei Fetissov from Rouen University, France said:

"These early data are intriguing, and worthy of further investigation. At the moment it would be premature to ascribe a direct role of gut bacteria in the action of antidepressant drugs until this work can be reproduced in humans, which is what the authors now hope to do. The composition of gut microbiota is very sensitive to the metabolic processes of the body and can change naturally, through drug-induced metabolic shifts in the brain and other organs. Some of the changes reported here, for example increased Christensenella, can be indeed beneficial, but overall significance of drug-induced changes of bacterial composition on the metabolic and mental health needs further research.

This is an independent comment; Professor Fetissov was not involved in this work.

ENDS

Notes for Editors

European College of Neuropsychopharmacology (ECNP)

The ECNP is an independent scientific association dedicated to the science and treatment of disorders of the brain. It is the largest non-institutional supporter of applied and translational neuroscience research and education in Europe. Website: www.ecnp.eu

The 31st annual ECNP Congress takes place from 7th to 10th September in Copenhagen. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting up to 6,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Congress website: https://2019.ecnp.eu/

Conference abstract, Mon 9th Sept 12.15 pm poster 585

Differential effects of psychotropic drugs on microbiome composition

S. Cussotto1, C. Strain2, F. Fouhy2, R. Strain2, V. Peterson3, T. Bastiaanssen3, C. Long-Smith4, G. Clarke4, C. Stanton4, T. Dinan4, J. Cryan4
1APC Microbiome Ireland, Department of Anatomy and Neuroscience, Cork, Ireland
2APC Microbiome Ireland, APC Microbiome Ireland,, Ireland
3APC Microbiome Ireland, Anatomy and Neuroscience, Cork, Ireland
4APC Microbiome Ireland, APC Microbiome Ireland, Cork, Ireland

Background:
The gut microbiome plays crucial roles in the function of various physiological aspects in health and disease [1]. Despite substantial scientific focus on the role of gut microbiome in drug metabolism [2], there remains a critical lack of understanding of how psychotropic medications might affect the gut microbiome. Unravelling this aspect will provide new insight into the mechanism of action of these medications and will possibly identify the gut microbiome as new target for the treatment of certain psychiatric disorders.

Methods and results: Four different strategies have been employed to answer this scientific question. First, the impact of psychotropic medications on two bacterial strains resident in the human gut, Lactobacillus rhamnosus and Escherichia coli, has been analysed in vitro. Data were analysed using a mixed-design ANOVA followed by t-test. The two antidepressants fluoxetine and escitalopram displayed adose-dependent antimicrobial activity. Specifically, doses of 600 and 400 µg/mL fluoxetine had bactericidal effects on L.rhamnosus and E.coli [rep. measures ANOVA followed by t-test: all $p<0.05$ from 3h to 7h timepoint] while a dose of 100 µg/mL selectively inhibited the growth of E.coli [t-test: $p<0.05$ from 3h to 7h timepoint]. Escitalopram, at a dose of 600 µg/mL, significantly inhibited the growth of E.coli [t-test: $p<0.05$ from 4h to 7h timepoint].

Based on the in vitro data, we aimed at investigating the impact of a 4-week treatment with psychotropic drugs on the composition and richness of the microbiome in male adult Sprague-Dawley rats. Seven experimental groups (control,

escitalopram, venlafaxine, fluoxetine, lithium, valproate and aripiprazole; n=8 rats/group) received a chronic treatment in eitherchow or drinking water followed by 16S bacterial rRNA sequencing of the caecum content. Sequencing data were analysed usingKruskal-Wallis test followed by Mann-Whitney U test and corrected for multiple comparisons. Lithium, valproate and aripiprazole administration significantly increased microbial richness and diversity [Kruskal-Wallis test for Chao1 p=.000; Mann-Whitney testU(16)=6, p=.006; U(16)=10, p=0.021; U(16)=12, p=0.036 respectively], while the other treatments did not differ from controls.

At the genus level, several species belonging to Clostridium, Peptoclostridium, Intestinibacter and Christensenellaceae among others, were increased following treatment with lithium, valproate and aripiprazole when compared to the control group [allp<0.05 for Mann-Whitney U test].With a translational approach, the authors are currently working on a large-scale human cohort where the microbiome composition of patients undertaking psychotropic drugs will be investigated and functional analysis will be carried out. The last aim of this project is to analyse the faecal microbiome of depressed patients pre- and post- antidepressant administration and to examine whether the microbial composition correlates with drug efficacy/response.

Conclusion: These data show that the antidepressants fluoxetine and escitalopram have specific antimicrobial activity in vitro and that certain psychotropic medications influence the composition of the gut microbiome in vivo. Overall, unravelling the impact of psychotropics on the gut microbiome offers the potential to provide critical insight into the mechanism of action and side effects of these medications, suggesting that precision medicine strategies should include the intestinal microbiome as a potential treatment modifier [3].

References

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