Media Release: European College of Neuropsychopharmacology

New research shows fish intake associated with boost to antidepressant response

Embargo until: 00.01 Monday 20th October (Central European Summer Time, Berlin)

Berlin, 20 October 2014 Up to half of patients who suffer from depression (Major Depressive Disorder, or MDD) do not respond to treatment with SSRIs (Selective Serotonin Reuptake Inhibitors). Now a group of Dutch researchers have carried out a study which shows that increasing fatty fish intake appears to increase the response rate in patients who do not respond to antidepressants. This work is being presented at the European College of Neuropsychopharmacology congress in Berlin.

According to lead researcher, Roel Mocking (Amsterdam):

"We were looking for biological alterations that could explain depression and antidepressant non-response, so we combined two apparently unrelated measures: metabolism of fatty acids and stress hormone regulation. Interestingly, we saw that depressed patients had an altered metabolism of fatty acids, and that this changed metabolism was regulated in a different way by stress hormones".

The researchers were looking at the relationship between depression and fatty acids, and various hormones, including the stress hormone cortisol. They took 70 patients with depression and compared them to 51 healthy controls, by measuring their fatty acid levels and cortisol levels. They then gave the depressed patients 20mg of an SSRI daily for 6 weeks, and in those who did not respond to the SSRIs the dose was gradually increased up to 50mg/day. Fatty acid and cortisol levels were measured during the trial.

They found that the MDD patients who didn't respond to the SSRI also tended to have abnormal fatty acid metabolism, so they checked the dietary habits of all those taking part in the trial. Fatty fish is rich in fatty acids, such as the well-known Omega-3 DHA. So the researchers looked at the amount of fatty fish in the diet of all involved in the trial. They categorised the patients into 4 groups, according to their fatty fish intake, and they found that those who took the least fish tended to respond badly to anti-depressants, whereas those who had most fish in the diet responded best to anti-depressants. Those who ate fatty fish at least once a week had a 75% chance of responding to antidepressants, whereas those who never ate fatty fish had only a 23% chance of responding to antidepressants.

Roel Mocking continued:
"This means that the alterations in fatty acid metabolism (and their relationship with stress hormone regulation) were associated with future antidepressant response. Importantly, this association was associated with eating fatty fish, which is an important dietary source of

omega-3 fatty acids. These findings suggest that measures of fatty acid metabolism, and their association with stress hormone regulation, might be of use in the clinic as an early indicator of future antidepressant response. Moreover, fatty acid metabolism could be influenced by eating fish, which may be a way to improve antidepressant response rates".

"So far this is an association between fatty acids in blood and anti-depressant response; so it's not necessarily a causal effect. Our next step is to look at whether these alterations in fatty acid metabolism and hormonal activity are specific for depression, so we are currently repeating these measurements in patients with post-traumatic stress disorder and schizophrenia".

ECNP President, Professor Guy Goodwin (Oxford) said:

'Understanding non-response to treatment with SSRIs remains an important known unknown. There is already an intriguing association between eating fish and general health. The present study, while preliminary, takes the story into the realm of depression. Larger scale definitive studies will be of considerable interest".

Ends

Notes for editors

Please mention the European College of Neuropsychopharmacology Berlin Congress in any story resulting from this press release

Contacts

Mr Roel Mocking can be reached via r.j.mocking@amc.uva.nl
Professor Guy Goodwin can be reached via: guy.goodwin@psych.ox.ac.uk
ECNP Press Officer, Tom Parkhill, can be reached at press@ecnp.eu or on phone number +39 349 238 8191.

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.

ECNP organises a wide range of scientific and educational activities, programmes and events across Europe, promoting the exchange of high-quality experimental and clinical research and fostering young scientists and clinicians.

The annual ECNP Congress takes place from 18-21 October. It is Europe's premier scientific meeting for disease-oriented brain research, annually attracting between 5,000 and 8,000 neuroscientists, psychiatrists, neurologists and psychologists from around the world. Website: www.ecnp.eu

This research has been funded by a grant from the Netherlands Organization for Health Research and Development (ZonMw), program Mental Health, education of investigators in mental health (OOG; #100-002-002) to H.G. Ruhé, a grant from the Dutch Brain Foundation (14F06.45), and a personal grant from the Academic Medical Center, University of Amsterdam to R J Mocking.

ABSTRACT P.2.b.031 – Presented Monday 20th October, 11.45 (CEST).

Longitudinal interplay between paroxetine response, cortisol and fatty acid metabolism in major depressive disorder

R.J.T. Mocking[1 ◦], H.F. Verburg[1], A.M. Westerink[1], J. Assies[1], F.M. Vaz[2], M.W.J. Koeter[1], H.G. Ruh'e[3], A.H. Schene[4] *[1]Academic Medical Center, Psychiatry, Amsterdam, The Netherlands; [2]Academic Medical Center, Laboratory Genetic Metabolic Disease, Amsterdam, The Netherlands; [3]University Medical Center, Psychiatry, Groningen, The Netherlands; [4]Radboud University Medical Center, Psychiatry, Nijmegen, The Netherlands*

Background: If we better understand what factors explain antidepressant response, we might (I) influence these factors to improve response rates, (II) measure them to monitor treatment response, and (III) use these factors to select the optimal treatment for each individual patient. Two factors that may be involved in antidepressant response are fatty acid (FA)-metabolism and the hypothalamic–pituitary–adrenal (HPA)-axis. These systems and their relation have been reported to be altered in major depressive disorder (MDD); moreover, preclinical evidence suggests a longitudinal interplay with antidepressant-treatment, which has not been clinically studied before [1−3]. **Purpose:** We aimed to test whether alterations in FAmetabolism, and its relationship with the HPA-axis, would (I) predict, and/or (II) change during, paroxetine response. Finally, we expected that (III) randomized paroxetine dose-escalation would normalize alterations in FA-metabolism compared to placebo. **Methods:**We compared 70 initially unmedicated MDD-patients with 51 matched controls, regarding erythrocyte membrane FAs and their relationship with salivary cortisol [2−3]. Subsequently, we treated MDD-patients with 6 weeks 20 mg/day selective serotonin reuptake inhibitor (SSRI) paroxetine, followed by a 6-week randomized, double-blind, placebo-controlled dose-escalation up to 50 mg/day in patients not responding at week 6, while repeating FA- and cortisol measures. We performed analyses using linear mixed models in SPSS 20 (IBM). **Results:** Also after correction for confounders, MDD-patients had higher FA-chain length, -unsaturation and -peroxidation, and arachidonic acid (AA) concentrations than controls (b=7.84, 95% CI = 2.84, 12.84, F = 9.66, p = 0.002, Cohen's d=0.671). In addition, patients showed more negative relationships of FAunsaturation and -peroxidation with cortisol. Moreover, these FAalterations and more negative relationships with cortisol were associated with paroxetine non-response. Specifically, within the patients, non-responders had higher AA-concentrations (b = 8.68, 95% CI = 2.02–15.33, F = 5.49, p = 0.007) and lower eicosapentaenoic acid/AA-ratios (b = −0.43, 95% CI = −0.84, −0.02, F = 4.02, p = 0.024) than both late- and early-responders during the entire study. Non-response was also associated with low omega-3 docosahexaenoic acid (DHA) (b = −5.64, 95% CI = −9.14, −2.14, F = 4.48, p = 0.016), which was mediated by fish intake. Furthermore, response was associated with time-courses of FA-chain length (p = 0.029), -peroxidation (p = 0.006) and omega-3 eicosapentaenoic acid (EPA) ($p<0.05$): early responders started low and increased over time, while non-responders exhibited opposite patterns. Randomized paroxetine dose-escalation had no effect on FA-metabolism nor its relation with the HPA-axis. **Conclusions:** These new data corroborate that alterations in FA-metabolism and its relationship with the HPA-axis are involved in MDD-pathophysiology.

Furthermore, FA-alterations and their relationship with the HPA-axis predicted antidepressant nonresponse, suggesting a modifying effect on paroxetine effectiveness. In addition, specific changes in FA-metabolism over time were associated with treatment response, indicating that FAs mediate paroxetine's working mechanisms. Considering that omega-3/AA FA-ratio is involved in inflammatory regulation [1], our results support an inflammatory component underlying MDD and non-response. An influence of fish intake suggests that FAmetabolism may be a potentially modifiable target to improve antidepressant response rates. In conclusion, alterations in FAmetabolism, and its relationship with cortisol, are associated with paroxetine response in MDD, and may consequently provide novel targets for (I) biomarkers to predict and monitor, or (II) (add-on) treatment to improve, antidepressant response-rates, e.g. in a personalized medicine setting. **References**

[1] Assies, J., Mocking, R.J., Lok, A., Ruh′e, H.G., Pouwer, F., Schene, A.H., 2014. Effects of oxidative stress on fatty acid- and onecarbon-metabolism in psychiatric and cardiovascular disease comorbidity. Acta Psychiatr Scand (Epub phead of print) doi: 10.1111/acps.12265. [2] Mocking, R.J., Ruh′e, H.G., Assies, J., Lok, A., Koeter, M.W., Visser, I., Bockting, C.L., Schene, A.H., 2013. Relationship between the hypothalamic–pituitary–adrenal-axis and fatty acid metabolism in recurrent depression. Psychoneuroendocrinology 38, 1607–1617. [3] Mocking, R.J., Assies, J., Lok, A., Ruh′e, H.G., Koeter, M.W., Visser, I., Bockting, C.L., Schene, A.H., 2012. Statistical methodological issues in handling of fatty acid data: percentage or concentration, imputation and indices. Lipids 47, 541–547.