

Press release: European College of Neuropsychopharmacology

## ***Nicotine dose in a single cigarette blocks estrogen production in women's brains***

Not peer reviewed/experimental study/people

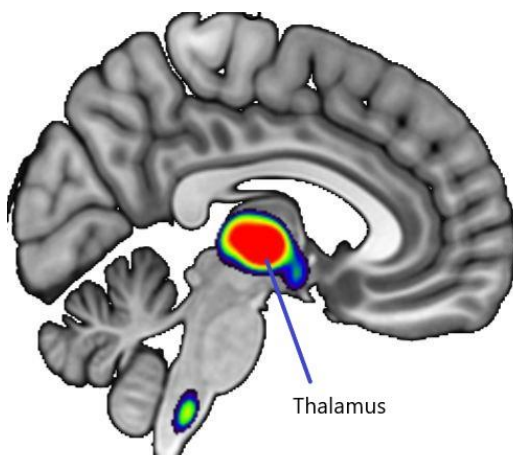
**Embargo until: 00.05 CEST (Vienna), Monday 17<sup>th</sup> October 2022**

A dose of nicotine, equivalent to that found in a single cigarette blocks estrogen production in women's brains. This may explain several behavioural differences in women who smoke, including why they are more resistant than men to quitting smoking. This work is presented for the first time at the ECNP Congress in Vienna.

Lead researcher, Associate Professor Erika Comasco (Uppsala University, Sweden) said:

*“For the first time, we can see that nicotine works to shut down the estrogen production mechanism in the brain of women. We were surprised to see that this effect could be seen even with a single dose of nicotine, equivalent to just one cigarette, showing how powerful the effects of smoking are on a woman's brain. This is a newly-discovered effect, and it's still preliminary work. We're still not sure what the behavioural or cognitive outcomes are; only that nicotine acts on this area of the brain, however we note that the affected brain system is a target for addictive drugs, such as nicotine”.*

The effect has been shown in the thalamus, which is part of the limbic system in the brain. This system is involved in behavioural and emotional responses.



*Illustration: Aromatase (estrogen synthetase) detected in the thalamus (red spot) (credit: Jana Immenschuh)*

The researchers, from Uppsala University in Sweden, worked with a group of ten healthy female volunteers. The women were given a commercially available nicotine dose intranasally, and at the same time were injected with a radioactive tracer attached to a molecule which binds to the enzyme aromatase: aromatase, also known as estrogen synthase, is the enzyme responsible for the production of estrogen. MRI and PET brain scans enabled the researchers to visualise both the quantity of aromatase, and where it was located in the brain. The researchers found that a single dose moderately reduced the amount of aromatase in the brain.

It has been known for some time that women and men respond differently to nicotine, with women being more resistant to nicotine replacement therapy, and showing a greater tendency than men to relapse when trying to quit smoking. However, the biological basis for these differences is not understood. This is the first time that this inhibitory effect on aromatase production has been shown in humans. The effect on men was not studied.

Professor Comasco continued *“This discovery leads us to believe that nicotine’s effect on estrogen production has a significant impact on the brain, but perhaps also on other functions, such as the reproductive system – we don’t know that yet. There are significant differences in the way men and women react to smoking. Women seem to be more resistant to nicotine replacement therapy, they experience more relapses, show greater vulnerability for heritability of smoking, and are at greater risk of developing primary smoking-related illnesses, such as lung cancer and heart attacks. We need now to understand if this action of nicotine on the hormonal system is involved in any of these reactions.*

*Of course this is a comparatively small group of women, we need a larger sample to confirm these findings. Nevertheless, the message is that nicotine has various effects on the brain, including on the production of sex hormones such as estrogen”.*

Commenting, Professor Wim van den Brink, Emeritus Professor of Psychiatry and Addiction at the Academic Medical Center, University of Amsterdam said:

*“This is indeed an important first finding. Smoking has many adverse effects in men and in women, but this particular effect of nicotine on the reduction of estrogen production in woman was not known before. It should be noted, however, that tobacco addiction is a complex disorder with many contributing factors. It’s unlikely that this specific effect of nicotine on the thalamus (and the production of estrogen) explains all the observed differences in the development, treatment and outcomes between male and female smokers. It is still a long way from a nicotine induced reduction in estrogen production to a reduced risk of nicotine addiction and negative effects of treatment and relapse in female cigarette smokers, but this work merits further investigation”.*

Professor van den Brink was not involved in this work, it is an independent comment.

*This work is presented at the 35<sup>th</sup> European College of Neuropsychopharmacology annual conference, which takes place in Vienna and online from 15-18 October, see <https://www.ecnp.eu/Congress2022/ECNPcongress>. Up to 5000 delegates are expected to attend. The ECNP is Europe’s main organisation working in applied neuroscience.*

\*Press release labelling system for journalists, see <https://tinyurl.com/3kww75hy> for details

## **Notes for Editors**

### **Conference abstract**

#### **P.0346 Nicotine’s effect on in vivo estrogen synthase binding in the limbic brain**

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A wealth of studies suggests sex differences in psychiatry but their psychoneuroendocrine underpinnings remain largely unknown. Men are up to twice as likely as women to develop substance use disorders, yet women are less successful at quitting. Women seem to be more resistant to nicotine replacement therapy and experience more relapses, though the prevalence of nicotine abuse is greater in men. The behavioural effects of nicotine are mediated by nicotinic acetylcholine receptors, but recently an additional pathway involving sex steroids has been suggested. Smoking women enter menopause earlier and have lower plasma estrogen levels pre-menopause than non-smokers. Sex and steroid hormones exert a modulatory role on the reward effect of nicotine throughout a somewhat complex interplay with the dopaminergic system. Nicotine was found to inhibit estrogen synthase *in vitro* and *in vivo* in foetal and neonatal rodents, similarly its metabolite cotinine. Estrogen synthase is the enzyme that acutely and chronically regulates the synthesis of estrogens, and is highly expressed in the limbic brain. A [<sup>11</sup>C]cetrozole positron emission tomography (PET) study in female baboons showed that nicotine interacts with brain estrogen synthase by inhibiting its availability in the amygdala and striatum, while lower levels of estrogen synthase were found in the human brain of four smokers versus non-smokers. The inhibition of estrogen synthase may be an alternative pathway by which nicotine affects behaviour, particularly where such effects are sexually dimorphic. Thus, we sought to investigate limbic estrogen synthase availability in relation to exposure to nicotine in healthy, non-smoking, naturally cycling women. The present study included a structural magnetic resonance imaging, and two PET scans combined with [<sup>11</sup>C]cetrozole was performed to assess the availability of estrogen synthase in healthy women. Before one of the two neuroimaging sessions, the dose of nicotine contained in one cigarette was administered by spraying twice 0.5 mg of Nicorette® nasal spray in the nostrils. PET preprocessing was carried out with SPM8 and PVELAB. [<sup>11</sup>C]cetrozole binding potential maps were generated using reference Logan analysis with the cerebellum as the reference region [1]. Gonadal hormone levels were assessed using mass spectrometry. Voxel-wise, whole-brain, paired-t-test in SPM, using the non-parametric Threshold Free Cluster Enhancement (TFCE) permutation method were performed. High availability of estrogen synthase was found in the thalamus, hypothalamus, and amygdala. Estrogen synthase binding in the ventral thalamus was lower upon nicotine exposure ( $p < 0.1$ , FWE; TFCE). These results were confirmed by a region-of-interest based approach pointing to diminished levels of estrogen synthase in both the right and left thalamus ( $p < 0.05$  uncorrected). The present findings corroborate the ones on monkeys, though they indicate species-specific effects in terms of brain regions affected by nicotine. This nicotine-estrogen synthase interaction in humans suggests a putative mechanism mediating the effects of nicotine.

## References

[1] Jonasson, M., Nordeman, P., Eriksson, J., Wilking, H., Wikström, J., Takahashi, K., Niwa, T., Hosoya, T., Watanabe, Y., Antoni, G., Sundström Poromaa, I., Lubberink, M., Comasco, E. 2020 Quantification of aromatase binding in the female human brain using [<sup>11</sup>C]cetrozole positron emission tomography *J Neurosci Res* Nov;98(11):2208-2218. doi: 10.1002/jnr.24707.

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