Case report

Nicotine augmentation for refractory obsessive-compulsive disorder. A case report

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Abstract

The authors present a case of obsessive-compulsive disorder (OCD) resistant to conventional treatments, which improved following nicotine augmentation administered as 4 mg chewing gum. The role of acetylcholine in the pathophysiology of OCD is not clear. The authors discuss the effect of nicotine on memory for actions.
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1. Introduction

Recent neurobiological data on obsessive compulsive disorder (OCD), obtained with sophisticated technology, are more and more specific. Strong evidence from functional neuroimaging studies indicates that there are orbital cortex and basal nucleus alterations in some OCD patients (Saxena et al., 1998; Adler et al., 2000; Alptekin et al., 2001), although its interpretation is controversial. While the etiologic nature of the observed alterations remains to be proved, a pathogenetic explanation seems more likely.

It is already known that serotonergic systems are not the only systems involved in OCD; moreover, clomipramine will remain the gold standard in OCD treatment due to its non-selective mechanism of action. Carlsson (2001) focused attention on glutamatergic balance and cholinergic system. Although the glutamatergic hyperactivity hypothesis in OCD is far from being elucidated, several data sets have been collected on the interaction between cholinergic and glutamatergic system (Heresco-Levy and Javitt, 1998; Girod et al., 2000; Vogt and Regehr, 2001; Araki et al., 2002; Mansvelder et al., 2002). These studies suggest that nicotine acts both by facilitating glutamatergic transmission and stabilizing the glutamatergic hyperactivity of the loop running from the orbitofrontal cortex to the cyngulate gyrus, the striatum and the thalamus. Several mechanisms may account for distinct profiles of glutamatergic neurotransmission facilitation elicited by nicotinic agonists at a variety of synapses, and they cannot be understood simply by considering direct effects on excitatory presynaptic terminals. Differences in the subunit composition of presynaptic nAChRs may contribute to distinct profiles of synaptic facilitation elicited by nicotine (Girod et al., 2000; Vogt and Regehr, 2001). The intracellular mechanism of glutamatergic facilitation is mediated by calcium influx via direct and indirect pathways. Mansvelder et al. (2002) reported that nicotine can enhance glutamatergic transmission, while the nAChRs on GABA neurons are desensitized, thus shifting the balance of synaptic inputs to excitation.

Carlsson (2001) supported her model by the observation of clinical improvement after nicotine addition in an OCD patient resistant to conventional pharmacological treatments.

Here we report a similar experience with a young OCD patient.

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2. Case report

P.A. is a 31-year-old male patient with psychiatric family history of affective disorder and a 16-year history of OCD. The obsessions were mainly sexual and the compulsion consisted in the need to verbalise the thoughts. As a child, he had motor and speech retardation and recurrent tonsillitis. He attended secondary school until the age of 14, and never worked after that, due to his psychopathological disorder. Starting at 20 years of age, he received several pharmacological treatments with modest results. Six months treatment with fluvoxamine at 350 mg produced only a partial decrease of compulsions, and the picture remained substantially unchanged with the addition of haloperidol and clozapine. No improvements were obtained with risperidone (4 mg) added to sertraline (250 mg), or with olanzapine (15 mg) added to sertraline. Best results were obtained with clomipramine (250 mg) and valproic acid (1 gr); but after 8 months of such treatment, the side effects were no longer tolerated by the patient. Clonazepam was ineffective. Based on Carlsson's paper, we proposed 4 mg nicotine chewing gum in addition to the current treatment with clomipramine 200 mg and valproate (1 gr).

Prior to treatment, he scored 38 on Yale-Brown Obsessive Compulsive Scale (Y-BOCS), 35 on the Global Assessment Scale and 6 on Clinical Global Impressions (CGI). He and his relatives returned for a follow-up visit after 4 weeks of treatment and were very enthusiastic about the results; compulsions had dramatically decreased both in frequency and in severity, his Y-BOCS score had fallen to 23 and his CGI score to 2. Greatest improvement was observed for the following Y-BOCS items: interference from obsessions, distress from obsessions, time spent for compulsions, interference from compulsions, distress from compulsions and resistance to compulsions. The patient was treated for an additional 3 months without reporting side effects; moreover, the addition of nicotine to his treatment allowed a reduction in clomipramine and valproate doses.

3. Discussion

Nicotine's mechanism of action on OCD symptoms is not easy to explain.

AChRs at presynaptic terminals or at preterminal locations have been shown to enhance the release of various neurotransmitters. The effect of cholinergic stimulation on the glutamate systems is very heterogeneous, because hyperglutamatergia causes different effects in regard to the target of postsynaptic glutamatergic neurons. It has been demonstrated that nicotine enhances glutamatergic transmission through nAChRs desensitisation and transiently enhances GABAergic transmission, leading to a reduction of inhibitory inputs due to nAChR (Mansvelder et al., 2002). In addition, local application of nicotine to the striatum produces an increase in the extracellular level of glutamate (Araki et al., 2002). Experimental studies suggested spatial and temporal differences in nicotine receptors activity on both excitatory and inhibitory neurons (Mansvelder et al., 2002). Furthermore, it has been shown that nicotine directly enhances hippocampal serotonin release (Kenny et al., 2000). Kenny et al. (2000) suggested that nicotine causes an increase in 5-HT release by acting on 5-HT terminals and a reduction in release by stimulating ACh discharge, which has an inhibitory action on 5-HT terminals.

Carlsson (2001) argued that a possible mechanism of the effect of nicotine on compulsions might be a reduction of acetylcholine release in the striatum, and a decrease of orbitofrontal cortex hyperglutamatergia. Recently, orbitofrontal cortex activation has also been found in nicotine craving (Brody et al., 2002). Moreover, Tizabi et al. (2002) reported that nicotine attenuates some symptoms of compulsive checking in a rat model of OCD.

We propose an alternative interpretation, taking into account the role of nicotine on memory functions. Current evidence suggests that there are deficits in non-verbal memory and memory for actions in OCD patients (Sher et al., 1984; Zitterl et al., 2001; Okasha et al., 2000; Tallis et al., 1999).

More specifically, several studies suggest that patients affected by OCD have low confidence in their own memories (Tolin et al., 2001). Moreover, it is well known that antiglutamatergic agents have negative effects on memory, while cholinergic transmission may represent the fundamental system.

On this basis, we suggest that nicotine effectiveness on compulsions, if confirmed, could be attributed to an improvement of memory for actions as well to a reduction of orbitofrontal activation, which also could be explained as a correlate of the lack of memory inputs.

4. Conclusions

The clinical observation of the effects of nicotine augmentation on a single patient affected by severe obsessive-compulsive disorder, although compatible with the hypothesis of an effect of nicotine on compulsions is, in itself, inconclusive. More observations from independent clinical studies of appropriate design and sample size are needed.

References

Adler, C.M., McDonough-Ryan, P., Sax, K.W., Holland, S.K., Arndt, S., Strakowski, S.M., 2000. fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive. J. Psychiatr. Res. 34, 317–324.

Alptekin, K., Degirmencib, B., Kivircika, B., Durakb, H., Yemez, B., Derebekb, E., Tunca, Z., 2001. Tc-99m HMPAO brain perfusion

SPECT in drug-free obsessive-compulsive patients without depression. Psychiatry Res.: Neuroimaging Section 107, 51–56.

Araki, H., Suemaru, K., Gomita, Y., 2002. Neuronal nicotinic receptor and psychiatric disorders: functional and behavioural effects of nicotine. Jpn J. Pharmacol. 88, 133–138.

Brody, A.L., Mandelkern, M.A., Edythe, D.L., London, E.D., Childress, A.R., Lee, G.S., Bota, R.G., Ho, M.L., Saxena, S., Baxter, L.R., Madsen, D., Jarvik, M.E., 2002. Brain metabolic changes during cigarette craving. Arch. Gen. Psychiatry 59, 1162–1172.

Carlsson, M.L., 2001. On the role of prefrontal cortex glutamate for the antithetical phenomenology of obsessive-compulsive disorder and attention-deficit hyperactivity disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 25 (1), 5–26.

Girod, R., Barazangi, N., McGehhe, D., Role, L.W., 2000. Facilitation of glutamateric neurotrasmission by presinaptic nicotinic acetylcholine receptors. Neuropharmacology 39, 2715–2725.

Heresco-Levy, U., Javitt, D.C., 1998. The role of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the pathophysiology and therapeutics of psychiatric syndromes. Eur. Neuropsychopharmacol. 8, 141–152.

Kenny, P.J., File, S.E., Neal, M.J., 2000. Evidence for a complex influence of nicotine acetylcholine receptors on hippocampal serotonin release. J. Neurochem. 75 (6), 2409–2414.

Mansvelder, H.D., Keath, J.R., McGehee, D.S., 2002. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 33, 905–919.

Okasha, A., Rafaat, M., Mahallawy, N., El Nahas, G., Seif El Dawla, A., Sayed, M., El Kholi, S., 2000. Cognitive dysfunction in obsessive-compulsive disorder. Acta Psychiatr. Scand. 101, 281–285.

Saxena, S., Brody, A.L., Schwartz, J.M., Baxter, LR., 1998. Neuroimaging and frontal–subcortical circuitry in obsessive-compulsive disorder. Br. J. Psychiatry 173 (Suppl. 35), 26–38.

Sher, K., Mann, B., Frost, R., 1984. Cognitive dysfunction in compulsive checkers: a further explanations. Behav. Res. Ther. 22, 493–502.

Tallis, F., Pratt, P., Jamani, N., 1999. Obsessive compulsive disorder, checking, and non-verbal memory: a neuropsychological investigation. Behav. Res. Ther. 37 (2), 161–166.

Tizabi, Y., Louis, V.A., Taylor, C.T., Waxman, D., Culver, K.E., Szechtman, H., 2002. Effect of nicotine on quinpirole-induced checking behavior in rats: implications for obsessive-compulsive disorder. Biol. Psychiatry 51, 164–171.

Tolin, D.F., Abramowitz, J.S., Brigidi, B.D., Amir, N., Street, G.P., Foa, E.B., 2001. Memory and memory confidence in obsessive-compulsive disorder. Behav. Res. Ther. 39 (8), 913–927.

Vogt, K.E., Regehr, G., 2001. Cholinergic modulation of excitatory synaptic transmission in the CA3 area of the hippocampus. J. Neurosci. 21, 75–83.

Zitterl, W., Urban, C., Linzmayer, L., Aigner, M., Demal, U., Semler, B., Zitterl-Eglesser, K., 2001. Memory deficits in patients with DSM-IV obsessive-compulsive disorder. Psychopathology 34, 113–117.