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### **Chronic N-acetylcysteine treatment promotes extinction of conditioned Cue-induced nicotine-seeking behaviour in the rat**

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Tobacco smoking is a chronic relapsing disorder and resumption is recurrent after abstinence. Although some pharmacological and psychosocial support can help smokers to quit, the high relapse rates indicate a need for more efficacious treatments. A large body of evidence indicates that the cysteine pro-drug N-acetylcysteine (N-AC) may have beneficial therapeutic effects in the treatment of drug addiction. In humans, pilot studies have shown that N-AC decreases cues-induced cocaine-craving, number of cigarettes smoked, marijuana use and craving. Pre-clinically N-AC reduced conditioned cues-induced cocaine- and heroin-seeking by restoring cystine-glutamate exchange, which normalizes extracellular glutamate (Glu), restoring tone on pre-synaptic inhibitory mGluR2/3 auto-receptors in the nucleus accumbens, thus blunting the increased Glu release associated with drug cues-induced reinstatement. Although nicotine-cues reinstate drug-seeking and increase extracellular Glu in the nucleus accumbens, it is still unclear whether N-AC would inhibit cue-induced nicotine-seeking. Moreover, it is unknown whether restoring Glu homeostasis by chronic N-AC treatment would enhance the outcome of cue-exposure therapy for smoking cessation. To gain such information, we used an animal model of cue-induced robust and lasting nicotine-seeking in abstinent rats after nicotine self-administration. We found that a single dose of N-AC (100 mg/kg) increased Glu extracellular release in the nucleus accumbens and induced a short-term reduction of cues-induced nicotine-seeking without altering cues-induced saccharin-seeking and rats' locomotor activity. Pre-treatment with LY341495 (1mg/kg), a selective mGluR2/3 antagonist completely prevented N-AC from reducing cues-induced nicotine-seeking behavior. When N-AC (100 mg/kg) was given chronically before daily lever-presses extinction, during abstinence or in combination with nicotine-associated cues induced re-instatement, it was found that only in the latter condition N-AC showed efficacy when bio-available during testing; furthermore N-AC also produced a long-lasting anti-relapse activity that was still present 2 weeks later. These results suggest that N-AC might offer a therapeutic opportunity in promoting extinction of nicotine-cue conditioned responding.

#### **Biography**

Cervo L, PhD is the Head of the Experimental Psychopharmacology Laboratory at IRCCS "Mario Negri" Institute for Pharmacological Research since 2006. From 1978 to 2001 he was a Research Fellow and then Chief of the Behavioural Pharmacology Unit in the Laboratory of Neuropharmacology at "Mario Negri" Institute. Between 1981 and 1983 he spent his Post-doc training in the Department of Psychiatry at the Chicago University, Illinois, U.S.A. From 1995 he was appointed "Student Supervisor" from the Cardiff University School of Biosciences and "Graduate Students Teacher" of the Pharmacological Research Specialist training program at the "Mario Negri" Institute. His research interests span the areas of behavioral neuroscience and psychopharmacology. His research mainly focuses on experimental animal models and their translational application to complex human disorders such as drug abuse, anxiety and depression. He is the author and co-author of several peer-review articles, communications in international meetings and is reviewer of several international scientific journals.

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