

## ORIGINAL INVESTIGATION

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## Dose-dependent stereoselective activation of the trigeminal sensory system by nicotine in man

Received: 16 March 1998/Final version: 14 September 1998

**Abstract** *Rationale:* Nicotine applied to the nasal cavity can evoke 'odorous' sensations in the concentration range near the detection threshold by the activation of the olfactory sensory system and at higher concentrations 'burning' and 'stinging' sensations by the dose-dependent recruitment of C- and A $\delta$ -fibers of the trigeminal sensory system. Neuronal nicotinic acetylcholine receptor (nAChR) subunits are expressed in trigeminal primary afferents and could constitute the receptors involved in nicotine perception. *Objective:* In the present study, we dose-dependently investigated the stereoselective effects of *R*(+)- and *S*(-)-nicotine on the trigeminal and olfactory sensory system in man. *Methods:* Trigeminal detection thresholds for the 'burning' and 'stinging' sensations and the olfactory detection threshold for the 'odorous' sensation were determined. In order to quantify trigeminal activation, we recorded summated electrical responses from the respiratory nasal mucosa during stimulation with *R*(+)- and *S*(-)-nicotine vapor (40, 80, 120, 160 ng/ml; stimulus duration: 250 ms). In addition, subjects rated the intensity of 'odorous', 'burning' and 'stinging' sensations. For chemical stimulation with nicotine enantiomers, a vapor-dilution olfactometer (constant flow rate: 140 ml/s, humidity: 80%, temperature: 37°C, stimulus duration 250 ms) was employed. *Results:* We found significant stereoselective differences for the trigeminal but not for the olfactory system, i.e. higher summated responses, higher trigeminal intensity estimates, and lower trigeminal detection thresholds for

*S*(-)- compared to *R*(+)-nicotine. *Conclusion:* Our results clearly demonstrate the different stereoselective activation of the trigeminal sensory system by *R*(+)- and *S*(-)-nicotine, indicating the presence of specific stereoselective receptors on trigeminal nociceptive A $\delta$ - and C-fibers.

**Key words** Nicotine · Stereoisomers · Sensory · Trigeminal · Olfaction · Pain

### Introduction

Stereospecific binding of nicotine enantiomers has been demonstrated for high and low affinity binding sites in the central nervous system, and in the periphery for binding sites at the nicotinic receptor of the autonomic and the somatic nervous systems (Meltzer et al. 1980; Romano and Goldstein 1980; Martin and Aceto 1981; Ikushima et al. 1982; Abood et al. 1985; Sloan et al. 1985; Aceto et al. 1986; Henley and Oswald 1987; Goldberg et al. 1989). The quantitative differences in binding values (IC<sub>50</sub>) of nicotine enantiomers seem to be small compared to the differences observed for the stereoisomers of opioids. Abood et al. (1985) found a threefold greater IC<sub>50</sub> value for *R*(+)-nicotine than for *S*(-)-nicotine at the higher affinity site and twice that at the lower affinity site. The affinity of opioids to the  $\mu$ 1-receptor was 10-fold higher for *R*(+)- than for *S*(-)-methadone (Kristensen et al. 1995). It has been shown in Dreiding models that the nitrogen atoms of the nicotine stereoisomers are nearly superimposable (Aceto et al. 1986), thus explaining the small stereoselective differences using the simplicity of the nicotine molecule. Nicotine itself resembles the structural properties of acetylcholine. The pyridine nitrogen of nicotine is an electron donor similar to the keto oxygen of the acetyl group of acetylcholine; the positive charge of the pyrrolidine nitrogen of nicotine is

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