UNEXPECTED SALIVARY SECRETORY EFFECTS OF SOME "ATYPICAL" ANTIPSYCHOTICS

- PRECLINICAL STUDIES ON CLOZAPINE, *N*-DESMETHYL-CLOZAPINE, AMISULPRIDE AND OLANZAPINE

Akademisk avhandling

Som för att avlägga odontologie doktorsexamen
vid Sahlgrenska akademin vid Göteborgs universitet
kommer att offentligt försvaras
på Odontologen, Medicinaregatan 12 E, Föreläsningssal 3
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av

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Avhandlingen baseras på följande arbeten:

I. **Clozapine: agonistic and antagonistic salivary secretory actions**
Ekström, J. Godoy, T. Riva, A
Journal of Dental Research 2010; 89: 276-280

II. ***N*-desmethylclozapine exerts dual and opposite effects on salivary secretion in the rat**
Ekström, J. Godoy, T. Riva, A
European Journal of Oral Sciences 2010; 118: 1-8

III. **Clozapine-induced salivation: interaction with *N*-desmethylclozapine and amisulpride in an experimental rat model**
Godoy, T. Riva, A. Ekström, J
European Journal of Oral Sciences 2011; 119: 275-281

IV. **Atypical antipsychotics - effects of amisulpride on salivary secretion and on clozapine-induced sialorrhea**
Godoy, T. Riva, A. Ekström, J
Oral Diseases 2012; 18: 680-691

V. **Salivary secretion effects of the antipsychotic drug olanzapine in an animal model**
Godoy, T. Riva, A. Ekström, J
Oral Diseases 2013; 19: 151–161

Abstract

Antipsychotics are generally associated with dry mouth and deterioration of the oral health. However, clozapine, the archetype of the atypical antipsychotics, is reported to induce not only mouth dryness but also, in about one-third of the patients, hypersalivation, the latter resulting in disturbed sleep, coughing and choking sensations during the night and drooling during the day. Nevertheless, the hypersalivation is questioned and, in some studies, related to a weakened swallowing reflex. Clinical studies are inconclusive and based on subjective drooling scores and indirect measurements of the saliva secreted. Preclinical studies on the effect of clozapine on the salivary flow are lacking. The aim of this *Thesis* was to explore the salivary secretory role of some atypical antipsychotics in an animal model, with clozapine-induced sialorrhea in focus. A secretory role for clozapine and its metabolite *N*-desmethylclozapine was established: saliva was secreted from duct-cannulated submandibular and parotid glands in the rat. The action was direct, independent on circulatory catecholamines and nerves, and mediated via muscarinic M_1 receptors. Together, the weaker agonist clozapine prevented its metabolite from exerting full agonistic effect. Thus, the sialorrhea in the clinic may be explained by a continuous bombardment of muscarinic M_1 receptors. At higher demands on the flow-rate, such as during a meal, the patient is, however, likely to experience insufficient salivation due to the clozapine/*N*-desmethylclozapine blockade of muscarinic M_3 and α_1 adrenergic receptors. Since clozapine/*N*-desmethylclozapine did not antagonize the β_1 adrenergic receptor, a sympathetic β_1-mediated salivary response can be expected to add to the muscarinic M_1 -mediated response during daytime; moreover stimulation of the two receptor types interacted positively. The antipsychotic drug amisulpride, reported to abolish the clozapine-induced sialorrhea, failed in the preclinical model. In contrast, it potentiated the secretory response to nervous activity as well as to autonomimetics, without causing secretion *per se*. Amisulpride exerted its effect at gland level but the mechanism is currently unknown. Amisulpride may be a potential drug for dry mouth treatment. Olanzapine, with a reported receptor profile similar to that of clozapine, evoked secretion, like clozapine but by other receptors, involving the substance P-type. In human salivary glands, acini but not vessels, lack substance P innervation. Therefore, olanzapine, in the clinic, is not a secretagogue via this receptor but may cause vasodilation and edema formation as a part of an inflammatory response.

Keywords: schizophrenia, atypical antipsychotics, sialorrhea, clozapine-induced sialorrhea, clozapine, *N*-desmethylclozapine, amisulpride, olanzapine, salivary secretion, muscarinic acetylcholine receptors, adrenergic receptors, non-adrenergic, non-cholinergic receptors, tachykinins
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