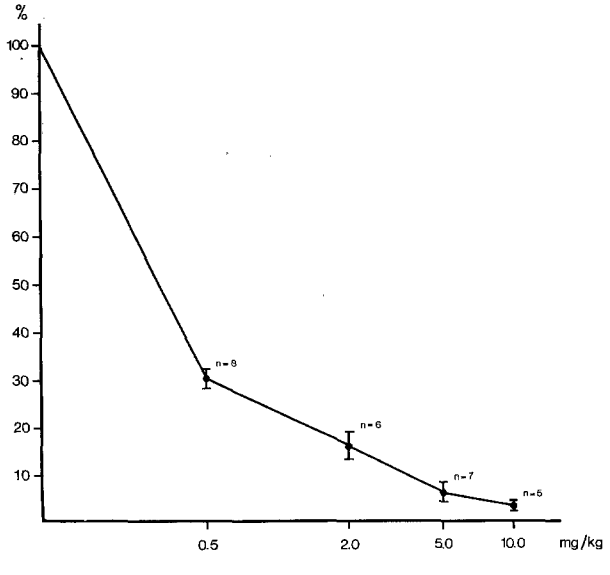
Effects of ICI 66082, a New β-Adrenoceptor blocking Drug, on the Submaxillary Gland of the Rat

The agent 4-(2-hydroxy-3-isopropylaminopropoxy) phenyl acetamine (ICI 66082) has been introduced as a new β-blocking substance, and as such reported to be cardioselective and no to be a partial agonist nor to have any membrane stabilizing properties[1,2]. In the rat submaxillary gland secretion in response to sympathetic stimulation is mediated via both α- and β-adrenoceptors, and the β-receptors are considered to be of the same type as those in the heart[3,4]. Therefore it was interesting to study the effects of ICI 66082 on the secretion from this gland.

Material and methods. Altogether 24 male albino rats of the Wistar strain weighing between 320 and 495 g were used. After induction with ether, a femoral vein was cannulated and the rat anaesthetized with chloralose (100 mg/kg i.v.). Continuous anaesthesia was ensured by injection of pentobarbitone (20 mg/kg i.p.) when needed. Tracheal cannula was inserted. The gland was exposed on either side in the neck and the duct was cannulated with a fine glass cannula. To elicit secretion, the following substances were given i.v.: methacholine (5 μg/kg), isoprenaline (2 and 10 μg/kg) and adrenaline (5 and 10 μg/kg). In 3 experiments, secretion was also evoked by stimulating the chorda-lingual nerve with supramaximal stimuli (4–8 V) and 2 msec duration at 2–5 impulses/sec. ICI 66082 was given i.v. in doses of 0.5, 2, 5 and 10 mg/kg. After injection of ICI 66082, 10 min elapsed before testing. Between each drug injection or nerve stimulation a pause of at least 5 min was allowed. The secretion produced was estimated as drops or fractions of drops. 1 drop corresponded to 18 μl. For statistical analysis Student's *t*-test was used.

Results and discussion. To see if ICI 66082 could cause any secretion of its own, the secretory response was studied during the first 10 min after administration. In 24 experiments there was no detectable secretion. In this respect, the substance differs from some other β-receptor blocking agents, dichloroisoprenaline, pronethalol and practolol which have the disadvantage of having a secretory effect[5,6].



The secretory effect of isoprenaline, 10 μg/kg, expressed in percent of maximal response for the dose given, after different doses of ICI 66082. Vertical bars represent S.E. of mean. All points of observation show statistical significance ($p < 0.01$).

The secretion elicited by isoprenaline was regularly found to be decreased after injection of ICI 66082. The secretory response to isoprenaline, 2 μg/kg, before injection of ICI 66082 was 5.7 ± 0.7 μl, mean ± S.E. of mean, ($n = 9$). When 0.5 mg of the blocking substance had been given the secretion was lowered to 1.6 ± 0.2 μl ($n = 6$) and after 5 mg/kg of ICI 66082 isoprenaline, 2 μg/kg, caused no secretion ($n = 5$). In both cases the differences are significant ($p < 0.001$ resp. $p < 0.001$). Isoprenaline, 10 μg/kg, gave a secretion of 14.8 ± 0.7 μl ($n = 14$). This was reduced by 0.5 mg/kg of the blocking substance to 4.8 ± 0.2 μl ($n = 6$) and by 5 mg/kg to 0.9 ± 0.2 μl ($n = 7$). Also these differences are significant ($p < 0.001$ resp. $p < 0.001$). 5 mg/kg of ICI 66082 completely abolished the secretory effects of isoprenaline, 10 μg/kg, in 2 experiments. In the Figure the effects of different doses of ICI 66082 on the response to isoprenaline, 10 μg/kg, are seen.

ICI 66082, 2 mg/kg, did not change the secretory response to chorda-lingual stimulation nor did 5 mg/kg of the substance given as a cumulative dose affect the chorda-lingual induced secretion. This indicates that the blocking agent is without any local anaesthetic effects.

Methacholine was tested before and after injection of the blocking substance. In 6 experiments the secretion remained unaltered. In 17 experiments a small rise was seen in response to a methacholine dose given 10 min after injection of ICI 66082. This rise was, however, not significant and when tested repetedly found not to last longer than half-an-hour.

The secretory effects of adrenaline varied when ICI 66082 had been given; in some experiments it was slightly lowered, in others unchanged or somewhat increased. Since adrenaline exerts its secretory action mainly via α-receptors but to some extent via β-receptors, it could be expected that a β-blocking drug should somewhat decrease the secretory response; this may, however, be more or less compensated for by the fact that when the β-receptors are blocked more of a submaximal dose of adrenaline may be available to act on the α-receptors.

In these experiments ICI 66082[7] was seen to have a blocking action on the β-adrenoceptors in the rat submaxillary gland, thus indicating these receptors to be of the same type as those in the heart. Further, its action seems to be exerted without partial agonist or local anaesthetic action as shown previously in the heart[1,2].

Zusammenfassung. Nachweis, dass die Substanz ICI 66082 eine β-Rezeptoren blockierende Wirkung in der Submaxillarisdrüse von Ratten hat. Weiterhin zeigen die Versuche, dass ICI 66082 ohne partielle Agonistenaktivität zu sein scheint und auch keine lokalanaesthetische Wirkung hat.

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