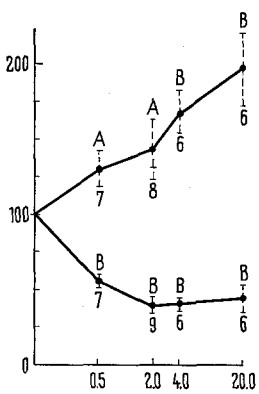
4(2-Hydroxy-3-isopropylaminopropoxy) Acetanilide as a β-Receptor Blocking Agent

An adrenergic β-receptor blocking compound 4(2-hydroxy-3-isopropylaminopropoxy) acetanilide (I.C.I. 50,172), acting selectively on receptors with excitatory effect was recently described by DUNLOP and SHANKS[1]. Some salivary glands have been shown to be supplied with β-receptors[2-5] and it was thought of interest to study the effect of the new β-blocking drug on such a gland, since the glandular receptors seem comparable with excitatory rather than inhibitory receptors in smooth muscle and heart.

Material and methods. The experiments were made on the submaxillary gland of the rat, which contains both α- and β-receptors. Altogether 27 rats were used. They were anaesthetized with chloralose (100 mg/kg) given through a cannula in a femoral vein after induction with ether. A tracheal cannula was inserted. The submaxillary duct was exposed in the neck, in 6 of the rats on both sides, and a fine glass cannula was introduced. To elicit secretion, standard doses of the following drugs were injected i.v. at intervals of 5 min: methacholine (5 μg/kg), adrenaline and isoprenaline (10 μg/kg). The amounts of saliva secreted were estimated as drops or fractions of drops. The size of the cannulae used was such that 1 drop corresponded to 11.5 μl.

Results and discussion. After i.v. injection of I.C.I. 50,172 in doses of 0.5–20 mg/kg the secretory effect of methacholine was regularly found to be increased. Methacholine alone caused a secretion of 9.1 ± 0.5 μl (n = 32). After 0.5 mg/kg I.C.I. 50,172 the response was increased to 11.9 ± 1.1 μl (n = 7) and after 4 mg/kg to 15.3 ± 1.3 μl (n = 6). The differences are significant at the $P < 0.05$ and < 0.001 levels, respectively. The Figure shows the increased responses to methacholine after different doses of I.C.I. 50,172 in per cent of the response obtained before this drug was administered.

The secretory responses to isoprenaline were regularly found to decrease after injection of I.C.I. 50,172. Before this drug had been given, isoprenaline caused a flow of 5.4 ± 0.5 μl (n = 31). After 0.5 mg/kg I.C.I. 50,172, the response was 3.0 ± 0.2 μl (n = 7) and after 4 mg/kg 2.2 ± 0.2 μl (n = 6). These differences are highly significant ($P < 0.001$). The responses to isoprenaline could, however, not be completely abolished. For instance, after 20 mg/kg I.C.I. 50,172 the secretory response to isoprenaline was 2.4 ± 0.5 μl (n = 6). In the Figure the effects of a series of doses of I.C.I. 50,172 on the responses to isoprenaline are shown.



Effects of different doses of I.C.I. 50,172 on the secretory responses to 5 μg/kg methacholine (upper part) and to 10 μg/kg isoprenaline (lower part). Abscissa: doses of I.C.I. 50,172 in mg/kg. Ordinate: secretory responses in per cent of those obtained before I.C.I. 50,172. A and B show the levels of significance, $P < 0.05$ and < 0.001, respectively. ± standard error of the mean and number of observations are also given.

A complicating factor in these experiments was the finding that I.C.I. 50,172 itself caused secretion of saliva, particularly in higher dosage. After doses below 5 mg/kg secretion was seen in some glands only, but above this level secretion was regularly obtained. Thus the flow during the first 10 min amounted to 0.8 ± 0.1 μl (n = 7) after 5 mg/kg and to 1.6 ± 0.5 μl (n = 7) after 20 mg/kg I.C.I. 50,172. The flow then gradually decreased but after a large dose of the drug it could continue for several hours. This secretion was not affected by i.v. atropine (1–10 mg/kg) or dihydroergotamine (0.5–2 mg/kg). It was reduced by propranolol and could even be abolished. The dose required (2–10 mg/kg) depended on the amount of I.C.I. 50,172 given.

The effect of I.C.I. 50,172 on the secretory responses to adrenaline varied from experiment to experiment. In some cases the response decreased, in others it increased or remained unchanged.

From these observations it can be concluded that I.C.I. 50,172 acts as a β-receptor blocking agent on the adrenergic receptors of the submaxillary gland cells in rats. Its use is, however, rendered difficult by the fact that it has in addition a secretory effect. This effect is obviously exerted on the β-receptors also. In this respect the drug resembles 2 other β-receptor blocking agents, dichloroisoproterenol and pronethalol[3]. A sympathomimetic effect of I.C.I. 50,172 on the heart has been described[1]. It is reasonable to explain the increased effect of methacholine after I.C.I. 50,172 as due to a combined sympathomimetic and parasympathomimetic secretory action. With adrenaline, varying effects of I.C.I. 50,172 can be obtained depending on whether the dominating action of I.C.I. 50,172 is to abolish the secretory effect of adrenaline on β-receptors or to add its secretory effect on β-receptors to that which adrenaline elicits on α-receptors. The secretory effect of the purely β-receptor stimulating isoprenaline, finally, is reduced by the I.C.I. 50,172, but it is conceivably difficult to observe complete blockage because of the slight secretory effect of I.C.I. 50,172[6].

Zusammenfassung. Nachweis, dass die synthetische Substanz 4(2-hydroxy-3-isopropylaminopropoxy)Acetanilid (I.C.I. 50,172) einen β-Rezeptoren-blockierenden Effekt auf die Submaxillardrüse der Ratte hat. Die Verwendung der Substanz wird allerdings durch eine gewisse sekretorische Wirkung reduziert.

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