Blockade of noradrenaline uptake and inhibition of gastric acid secretion by 2-[*p*-chlorophenyl-2-(pyridyl)-hydroxymethyl] imidazoline maleate (Sch-12650)

2-[*p*-Chlorophenyl-2 (pyridyl)hydroxymethyl] imidazoline maleate (Sch-12650) is as active in antidepressant tests in rats as the currently available antidepressants and possibly acts by interfering with catecholamine uptake mechanisms (Taber, Barnett & Roth, 1969). Imipramine is a blocker of noradrenaline uptake (Axelrod, Hertting & Potter, 1962) and also exhibits antigastric secretory activity (Bonfils, Dubrasquet & Lambling, 1962; Bass & Patterson, 1967; Lippmann, 1969). Similarly, 3,3-dimethyl-1-(3-methylaminopropyl)-1-phenylphthalan (Lu 3–010) has been shown to be effective both in blocking noradrenaline uptake (Waldeck, 1968; Lippmann, 1970b) and in inhibiting gastric acid secretion (Lippmann, 1970b). I have examined the effects of Sch-12650 on these activities.

The effects of intraperitoneally-administered Sch-12650 on the uptake and release of [^{3}H]noradrenaline (^{3}H–NA) in the heart of the rat are shown in Table 1. The animals (7–9 in each group) were injected with 2·5 μCi ^{3}H–NA (5·1 Ci/mM), intravenously, in 0·25 ml of 0·75% NaCl solution 45 min before or after the test compound and were killed 2 h after the test compound; ^{3}H–NA levels in the tissues were measured (Lippmann, 1969). Sch-12650 blocked the uptake, and did not cause an increased release, of ^{3}H–NA. The compound was similar in potency to imipramine as the ^{3}H–NA level was reduced to one-half by about 4 mg/kg of either compound.

Table 1. *Inhibition of uptake of [^{3}H]noradrenaline in the rat heart by Sch-12650 or imipramine given 45 min before or after the ^{3}H–NA*

Compound	Dose mg/kg, i.p.	Radioactivity content: counts/min g^{-1} ± s.e.	% Inhibition
Before ^{3}H–NA			
None	—	2761 ± 50 (P <0·001)	
Sch-12650 ..	10·0	775 ± 76 (P <0·001)	72
	5·0	1174 ± 57 (P <0·001)	57
	2·5	1871 ± 57 (P <0·001)	32
	1·25	2375 ± 109 (P <0·001)	14
Imipramine ..	5·0	781 ± 54 (P <0·001)	72
	2·5	1973 ± 162 (P <0·001)	29
After ^{3}H–NA			
None	—	2429 ± 48	
Sch-12650 ..	5·0	2554 ± 74	
	2·5	2622 ± 92	
Imipramine ..	5·0	2509 ± 115	

Table 2. *Inhibition of basal gastric acid secretion by Sch-12650 or imipramine*

Compound	Dose mg/kg, i.p.	Gastric acid secretion: m-equiv acid/ 3 h ± s.e. Exp. I	Exp. II	% Inhibition
None ..	—	0·33 ± 0·04	0·40 ± 0·04	
Sch-12650 ..	5·0	0·11 ± 0·03 (P <0·001)		65
	2·5	0·18 ± 0·01 (P <0·02)	0·22 ± 0·04 (P <0·01)	44, 46
	1·25		0·34 ± 0·07	
Imipramine ..	5·0	0·10 ± 0·03 (P <0·001)	0·13 ± 0·01 (P <0·001)	71, 69
	2·5		0·22 ± 0·07 (P <0·05)	46

Table 3. *Inhibition of pentagastrin-induced gastric acid secretion by Sch-12650 or imipramine*

Compound	Dose mg/kg	Gastric acid secretion	
		μ-equiv acid/ 2 h ± s.e.	% Inhibition
None	—	16 ± 1	
Pentagastrin (P)	0·001 (5×), s.c.	41 ± 8	
Sch-12650	5·0, i.p.	19 ± 2 (P <0·01)	88
+ P	0·001 (5×), s.c.		
Sch-12650	2·5, i.p.	30 ± 3	
+ P	0·001 (5×), s.c.		
Imipramine	10·0, i.p.	19 ± 3 (P <0·05)	88
+ P	0·001 (5×), s.c.		
Imipramine	5·0, i.p.	32 ± 2	
+ P	0·001 (5×), s.c.		

The effect of Sch-12650 on basal gastric acid secretion was measured using the Shay procedure (Shay, Sun & Gruenstein, 1954) as modified by Lippmann (1969). There were 8 animals in the control and 5–8 animals in each treated group. Sch-12650 inhibited the basal gastric acid secretion and at 2·5 mg/kg, intraperitoneally, decreased the gastric acid secretion to about one-half that of controls (Table 2). This activity was similar to that of imipramine.

In Table 3 are shown the effects of Sch-12650 on the induced increase in gastric acid secretion caused by pentagastrin (Lippmann, 1970a). There were 8 animals in the control and 6–8 in each treated group. Sch-12650 prevented the increase in gastric acid secretion at 5·0, but not at 2·5, mg/kg, intraperitoneally, while imipramine blocked the increase at 10, but not at 5, mg/kg. Thus, Sch-12650 was about twice as active as imipramine in preventing the pentagastrin-induced increase in gastric acid secretion.

Sch-12650 is similar to imipramine as it blocks uptake of noradrenaline and inhibits both basal and induced gastric acid secretion in the rat. The importance of the blockade of noradrenaline in relation to antisecretory activity of a drug has been previously discussed (Lippmann, 1970b). This compound has an advantage in that it does not antagonize acetylcholine (Taber & others, 1969), as does imipramine (Domenjoz & Theobald, 1959).

The author acknowledges the technical assistance of Mrs. S. Schaal, Miss D. Mulrooney, Miss A. Johnston and Miss F. Pollard. The author is grateful for gifts of drugs from the Schering Corp. (Sch-12650) and Geigy Ltd. (imipramine hydrochloride).

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February 3, 1970

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