Surface tension effects of β-adrenergic blocking drugs

SIR,—Some β-adrenergic blocking drugs have significant local anaesthetic or membrane effects, while others are devoid of this activity (Ariëns, 1967; Levy, 1968). This property appears to be unrelated to β-adrenergic blocking potency, although some parallelism between local anaesthetic actions and lipoid solubility was observed in a limited series of compounds (Levy, 1968).

In a search for mechanisms underlying the local anaesthetic effect of several of these compounds, their ability to lower surface tension of an aqueous solution was examined because a parallelism between the ability to lower surface tension of an aqueous solution and the local anaesthetic actions of a homologous drug series has been shown (Skou, 1954; Watson, 1960).

I now report an attempt to relate the surface tension lowering effect of five β-adrenergic blocking drugs with (*a*) their myocardial β-adrenergic blocking action, (*b*) chloroform–water partition ratio, (*c*) pK_a, and (*d*) their local anaesthetic properties.

The surface tension of the aqueous solutions was measured with a Fisher Tensiomat instrument (Model 21). Distilled water was used to dissolve the drugs. Solutions ranging from 0 (distilled water alone) to 200 mM were made daily. All determinations were made at 22–25°. Chloroform–water partition ratios and pK_a values for the compounds were obtained from previously published material (Levy, 1968). The technique yielded a mean value of the surface tension for distilled water of 72·7 dynes/cm. Surface tension was measured at least four times for each drug solution. Mean values were plotted *vs* the drug concentration (mM), using distilled water as reference.

The surface tension lowering effects of (±)-INPEA, (±)-MJ-1999 {4-[1-hydroxy-2′-(isopropylamino)ethyl]methane sulphonanilide hydrochloride}, (+)-INPEA, (±)-Kö-592 [1-(isopropylamino)-3-(*m*-tolyloxy)-2-propanol hydrochloride], (±)-pronethalol and (±)-propranolol are seen in Fig. 1. Table 1 relates this effect to other physicochemical and pharmacological actions. Several features are apparent from these data. (i) The highly lipid soluble agent (±)-propranolol produced the greatest lowering of surface tension, and the most hydrophilic compound (±)-MJ-1999 had the least effect, but the similar surface tension effects produced by (±)-Kö-592 and (±)-pronethalol rule out a conclusion that there is a simple relation between hydrophilicity and surface tension effects. Thus, Kö-592 has a chloroform–water partition ratio of 0·096 while pronethalol has a ratio of 15·0. INPEA, which has a surface tension lowering effect between that of MJ-1999 and pronethalol and Kö-592, has a

TABLE 1. SURFACE TENSION LOWERING EFFECTS OF β-BLOCKERS: RELATION TO PHYSICOCHEMICAL AND PHARMACOLOGICAL PROPERTIES

Compound	$\Delta\eta$[a] (dynes/cm)	$CHCl_3/H_2O$[b]	pK_a[b]	Relative[c]	
				Local anaesthesia (Cornea)	β-Blocking (Atrium)
(±)-Propranolol ..	−22·0	34·5	9·45	1·00	1·00
(±)-Pronethalol ..	−15·4	15·0	9·42	0·61	0·15
(±)-Kö-592	−12·9	0·096	8·57	0·57	1·19
(±)-INPEA	−5·9	1·29	8·82	0	0·04
(+)-INPEA	−3·4	1·29	8·78	0	0·002
(±)-MJ-1999 ..	0	0·03	8·26–9·89[d]	0	0·09

[a] Change in surface tension (dynes/cm) produced by 100 mM drug concentration (relative to water)
[b] Values taken from Levy (1968).
[c] Data from Levy (1968). Propranolol = 1·00.
[d] pK_a = 8·26 (ionization of sulphonamide group).
pK_a = 9·89 (ionization of amine HCl).

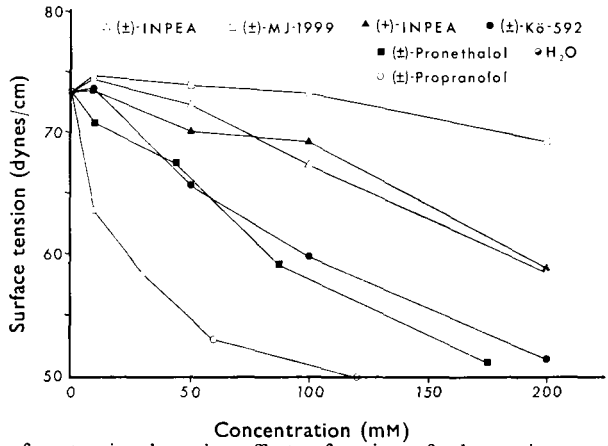

FIG. 1. Surface tension lowering effects of various β-adrenergic receptor blocking drugs.

chloroform–water ratio of 1·29. (ii) Optical isomerism apparently does not modify the surface tension effects of INPEA. (iii) The surface tension effect of these drugs is apparently unrelated to their *in vitro* myocardial β-adrenergic blocking potency. (iv) There is some parallelism between local anaesthetic activity and the ability of these compounds to lower surface tension. This is particularly evident for propranolol. Pronethalol and Kö-592, which are approximately equal in their local anaesthetic actions (rabbit cornea test) show similar effects in lowering surface tension. MJ-1999 and INPEA are devoid of local anaesthetic effects. Concentrations required to lower surface tension are many times higher than those producing myocardial β-blockade *in vitro* (Levy, 1968) but are related to concentrations used to demonstrate surface anaesthesia.

No apparent simple correlation exists between surface tension and β-adrenergic blocking potency. As with the chloroform–water partition ratio, there does appear to be some parallelism between surface tension effects and ability to produce local anaesthesia or depress myocardial contraction (Levy, 1968) for these compounds. While it is recognized that lowering surface tension (air–water) may merely signify the degree of non-wettability of the substance in solution, the marked differences in surface activity seen with agents having such diverse pharmacological and physicochemical properties as MJ-1999 and propranolol cannot be discounted. The hydrophilic methanesulphonanilide moiety characteristic of MJ-1999 yields a molecule with very low lipid solubility. An agent such as propranolol, which has a relatively high lipophilicity, may be surface-active by virtue of its ability to interact with the hydrogen-bonded water molecules. The predominantly non-polar characteristics of this molecule may result in it being positively adsorbed to the hydrogen-bonded water molecules with a concomitant orientation at the air–water interface. MJ-1999, with its predominant polar characteristic, would be negatively adsorbed, and as a result would be uniformly dispersed in the solution rather than orientated at the air–water interface.

The pronounced differences between such compounds as MJ-1999 and propranolol may be related to what Skou (1954) called "capillary activities" of local anaesthetic drugs. This property of being able to alter surface tension

activity therefore may be of importance in explaining the wide differences in pharmacological effects produced by β-adrenergic blockers represented by MJ-1999 and propranolol, particularly in their cell membrane actions.

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Hypotensive action of ephedrine in cats

SIR,—In the previous report (Maj & Langwiński, 1966) we described a temporary decrease of blood pressure in cats and rats after tachyphylaxis to tyramine. The depressor action of tyramine was regarded as being connected with the process of histamine liberation. Ephedrine belongs to the group of amines which cause tachyphylaxis. The purpose of the present paper was to find whether ephedrine causes a depressor action and if so, its mechanism of action.

The experiments were made on 40 cats anaesthetized with chloralose (80 mg/kg, i.p.) or urethane (1·5 g/kg, i.p.) accompanied by bilateral cervical vagotomy. Blood pressure was recorded from the carotid artery by a mercury manometer, respiration—with Marey's tambour, the kidney volume plethysmographically, and the contraction of the nictitating membrane recorded isotonically. All the substances were injected into a femoral or jugular vein. Ephedrine hydrochloride of specific rotation of $-33°$ to $-35·5°$ was used.

A hypotensive action of ephedrine in doses of 5 and 10 mg/kg was seen after tachyphylaxis was reached. The general dose of ephedrine averaged $8·9 \pm 1·9$ mg/kg. When such an average dose was administered, the additional dose of 5 mg/kg of ephedrine caused the depression of blood pressure of $14·6 \pm 1·4$mm Hg and the dose of 10 mg/kg caused the depression of the pressure $21·4 \pm 2·3$ mm Hg. Such a decreased blood pressure lasted 2–5 min. The depressive action of ephedrine was accompanied by the decrease of the kidney volume. During the hypotensive phase of ephedrine action, the contraction of the nictitating membrane was unchanged.

The type of anaesthesia, vagotomy, atropine (0·5 mg/kg), antazoline (10·0–30·0 mg/kg), cyclizine (2·0 mg/kg), methysergide (0·5–1·0 mg/kg), dichloroisoprenaline (5·0 mg/kg), propanolol (2 mg/kg) did not abolish or decrease the hypotensive action of ephedrine. Dihydroergotamine (1·0–2·0 mg/kg) and phentolamine (0·5–1·0 mg/kg) abolished the hypotensive action and decreased the kidney volume affected by ephedrine (5·0–10·0 mg/kg). Blackwell & Marley (1967) found that the hypotensive action of some amines depends on the values of the blood pressure in rats. Dihydroergotamine and phentolamine depressed the