brain tissue. Furthermore imipramine, in doses which antagonized the depression and hypothermia produced by noradrenaline, had no significant effect on this very low uptake. Thus it is impossible at this time to reconcile the observed antagonism of noradrenaline by imipramine-like antidepressants in the mouse with the current concept that these agents may facilitate central adrenergic mechanisms in the same way as they do at the periphery by inhibiting the uptake of noradrenaline into neurone transmitter stores (Axelrod & others, 1961; Iversen, 1965; Jori, Paglialunga & Garattini, 1966).

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May 20, 1966

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On the mechanism of the hyperglycaemic effect of chlorpromazine

SIR,—Chlorpromazine shows hyperglycaemic properties in several animal species including man. Previous experiments suggested that this drug interferes with the peripheral utilization of glucose (Chagovets & Shtutman, 1963; Jori, Bernardi & Garattini, 1964) as supported by the fact that chlorpromazine reduces glucose tolerance (Bhide, Tiwari & Balwani, 1965; Jori & Bianchetti, 1966). However, several mechanisms may be involved (Bonaccorsi, Jori & Garattini, 1964). In high doses, chlorpromazine may induce hyperglycaemia by activating adrenals and sympathetic nerve endings (Mraz & Triner, 1963).

Chlorpromazine also released adrenaline from adrenals *in vitro* (Weil-Malherbe & Posner, 1963) and it increased the urinary excretion of catecholamines *in vivo* (Johnson, 1964). Furthermore chlorpromazine impaired the uptake

TABLE 1. EFFECT OF β-ADRENERGIC BLOCKING AGENTS ON THE HYPERGLYCAEMIA INDUCED BY CHLORPROMAZINE AND BY ADRENALINE

Treatment mg/kg i.p.	Blood glucose (mg %) after chlorpromazine 15 mg/kg	Blood glucose (mg %) after adrenaline 100 µg/kg
Saline	137 ± 9	146 ± 3
MJ 1999 5 × 2	102 ± 2·6*	109 ± 2·4*
Propanolol 5 × 2	99 ± 5*	96 ± 4*
Pronethalol 5 × 2	116 ± 6·1*	112 ± 7·4
D-(−)-INPEA 10	108 ± 2*	106 ± 5*

Blood Glucose was measured 1 and 2 hr after adrenaline and chlorpromazine respectively.

* P <0·01 for saline treatment.

Untreated animals show a blood glucose level of 70 ± 5 mg %. β-Blocking drugs were given 1 hr before and 15 min after the administration of chlorpromazine or adrenaline. D-(−)-INPEA was given only 1 hr before the hyperglycaemic agent.

of catecholamines (Hertting, Axelrod & Whitby, 1961) making available more amine for the receptor sites.

This action may produce a different effect according to the receptor site involved (Thoenen, Hürlimann & Haefely, 1965). Chlorpromazine blocks the α- but not the β- adrenergic receptors. It may be that the hyperglycaemic effect of chlorpromazine, looked upon as a β-receptor effect, follows from the release of adrenaline. The following experiments support this view.

Sprague-Dawley rats, fasted for 16 hr, received a combination of non-hyperglycaemic doses of chlorpromazine (5 mg/kg i.p.) and 6 hr later an infusion of adrenaline (1·5 μg/kg) for 20 min. The resulting hyperglycaemia was more pronounced and longer lasting with the combination than for each drug. For example the concentration of blood glucose 10 min after the end of infusion was 154 mg % in chlorpromazine pretreated rats and 116 mg % with rats given only adrenaline.

In other experiments the effect of several β-adrenergic blocking agents was challenged on the hyperglycaemia obtained in 18 hr fasted rats by injection of 15 mg/kg i.p. of chlorpromazine or of 100 μg/kg s.c. of adrenaline. Blood glucose levels were measured by an enzymatic method (Hugget & Nixon, 1957).

The results in Table 1 show that the various β-blocking agents can prevent the hyperglycaemia induced either by chlorpromazine or adrenaline in fasted animals.

Acknowledgment. MJ 1999(4-(2-isopropylamino-1-hydroxyethyl)methanosulphonanilide) was kindly supplied by Mead Johnson, Evansville, Indiana; propranolol and pronethalol by I.C.I., London and D-(−)-INPEA (*N*-isopropyl-*p*-nitrophenylethanolamine) by Laboratorio Bioterapico Selvi, Milan.

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June 8, 1966

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