EFFECTS OF CHLORPROMAZINE, PROMAZINE, DIETHAZINE, RESERPINE, HYDROXYZINE, AND MORPHINE UPON SOME MONO- AND POLYSYNAPTIC MOTOR REFLEXES*

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The effects of chlorpromazine, promazine, diethazine, reserpine, hydroxyzine and morphine on some mono- and polysynaptic motor reflexes have been investigated in intact, spinal and decerebrate cats and rabbits. Chlorpromazine, promazine, reserpine and hydroxyzine selectively depress the monosynaptic spinal reflexes (knee jerk) of the intact animals. Polysynaptic reflexes (linguo-mandibular and crossed extensor) are slightly affected. In both cats and rabbits the brain of which was disconnected from the spinal cord by surgical sections at different levels, the inhibitory action of these drugs disappears. Morphine and diethazine, on the contrary, selectively depress the polysynaptic reflexes (linguo-mandibular) and in a minor degree the monosynaptic ones (knee jerk): this action is retained in spinal animals. These findings are discussed and related to other pharmacological properties of the compounds.

How chlorpromazine and reserpine affect the spinal reflex activity appears to depend upon experimental conditions. With reserpine, Schneider and colleagues[1] reported a facilitation of the monosynaptic responses in spinal and decerebrate cats, while Krivoy[2] observed a predominant inhibition of the monosynaptic transmission in the spinal cord of intact and decerebrate animals. Bein[3] reported that no inhibition of either mono- or polysynaptic reflexes occurred after reserpine. With chlorpromazine, Dasgupta and Werner[4] described an inhibition of the crossed extensor reflex in decerebrate cats: in the spinal animal this reflex was less affected. Preston[5], working on spinal cats, did not observe chlorpromazine to have any effect even in very high doses, on spinal reflex discharges recorded from the ventral roots. Krivoy[2] found a predominant inhibition of the monosynaptic transmission in intact and decerebrate animals. Bein[3] showed that the inhibition of mono- and polysynaptic spinal reflexes produced by chlorpromazine is suppressed after a transection of the cervical spinal cord.

In view of these contrasting results it seemed of interest to make a systematic reinvestigation of the actions of reserpine and chlorpromazine at the level of motor reflex activity in intact, spinal and decerebrate animals and a comparison of their effects with those of other related compounds.

EXPERIMENTAL

Methods

Twenty-two cats and 41 rabbits, of both sexes, weighing respectively 2–3 and 1·9–2·8 kg. were used.

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The knee jerk was elicited by tapping with a mechanical hammer the patellar tendon every 1 or 2 seconds. The linguo-mandibular reflex was obtained by stimulating the tongue through silver electrodes (square wave pulses; 100 cycles/sec.; 1 msec. duration) at the rate of one every 2 to 6 seconds. The crossed extensor reflex was elicited every 2 or 4 seconds by means of the stimulation (square wave pulse; 100 cycles/sec.; 0·5 msec. duration) of the central end of the contralateral sciatic nerve. The voltage was just above threshold. A Grass Model S4D stimulator with isolation unit was used. Reflex responses were kymographically recorded. Aqueous solutions of different concentrations were used.

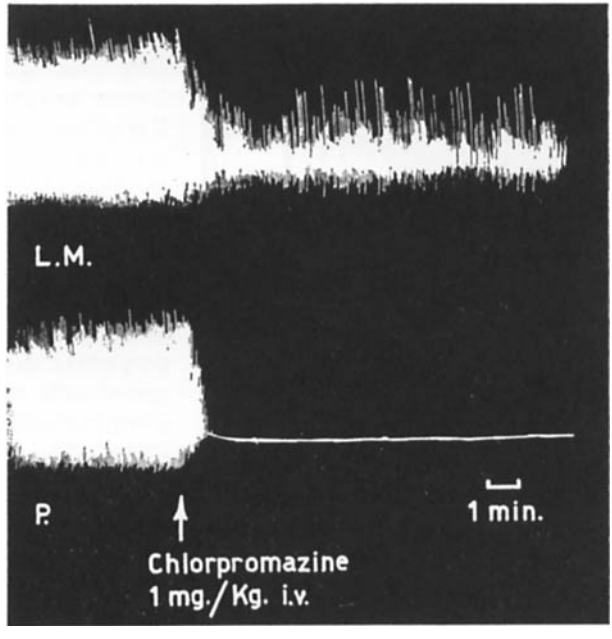

FIG. 1. Effects of chlorpromazine on linguo-mandibular (upper tracing) and patellar (lower tracing) reflexes. After 1 mg./kg. of chlorpromazine the knee jerk is suppressed and the linguo-mandibular reflex is decreased. Cat weighing 2·9 kg., anaesthetized with chloralose.

Solution of reserpine was prepared thus: reserpine 0·25 g., benzyl alcohol 2 ml., citric acid 0·25 g., propylene glycol 10 ml., distilled water to 100 ml.

In some experiments the blood pressure was recorded from the right common carotid artery.

In a first set of experiments intact animals were anaesthetized either with chloralose (70 mg./kg.) i.p. or urethane (1 g./kg. s.c.) or chloralose and urethane together (50 and 500 mg./kg.). By this procedure, eight of ten animals gave successful experiments. An additional group of animals was deeply anaesthetized with ether for section of the spinal cord (at cervical or lumbar level) or of the mesencephalon. Records were made

when the animals had recovered. In some experiments the spinal sections were made on animals previously anaesthetized with chloralose or urethane, to ascertain the effects of anaesthetics on spinal preparations. Here, six of ten experiments were successful.

RESULTS

From Table I, which presents our results, it may be seen that in the intact rabbit and cat, anaesthetized with chloralose and urethane or both, the patellar reflex is markedly inhibited by *chlorpromazine* in doses of 0·5–1·5 mg./kg. The onset of this action was quick and its duration very prolonged (Fig. 1: lower tracing). The linguo-mandibular reflex was markedly suppressed in 3 of 11 experiments (Fig. 1: upper tracing), in the others being unaffected or slightly inhibited. Figure 2 shows that mephenesin acts in an opposite manner. In spinal cats and rabbits, chlorpromazine may still inhibit the linguo-mandibular reflex, but it does not affect the knee jerk. After the chlorpromazine, a fall in the blood pressure (10–30 mm. Hg) was observed in both intact and spinal animals, but no clear relation exists between the hypotensive effect and degree of inhibition of the reflexes. With decerebrate rabbits, a slight inhibition of the patellar reflex was caused by the drug when the section was made at the intercollicular level, while after a pontine or prepontine section the effects disappeared.

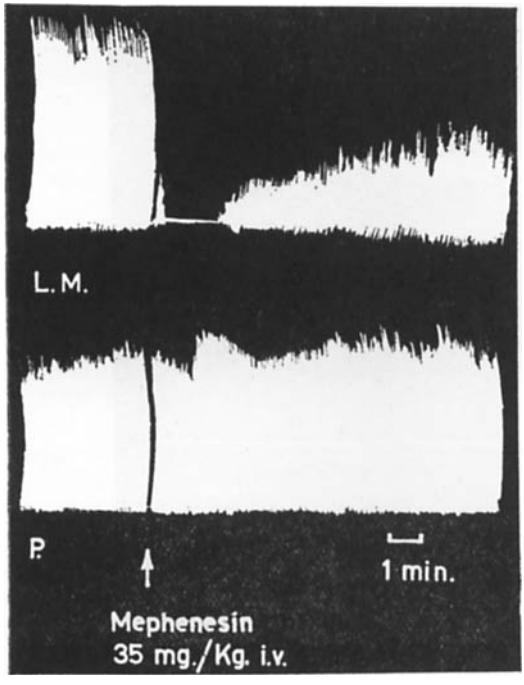

FIG. 2. Effects of mephenesin on linguo-mandibular (upper tracing) and patellar reflexes (lower tracing). After 35 mg./kg. of mephenesin the linguo-mandibular reflex is inhibited, while the patellar one is almost unaffected. Cat weighing 3 kg., anaesthetized with chloralose.

The effects of *reserpine* were studied on the linguo-mandibular, patellar and crossed extensor reflex and were different in rabbits and cats. After 0·4–1 mg./kg. the patellar reflex is slowly depressed in the intact rabbit, the decrease being usually complete in 15 minutes and lasting over two hours. In the intact cat the effects were less constant. In one experiment

no effect was observed after 2 mg./kg. In the others the inhibition sometimes lasted about one hour and often appeared after an initial facilitation of the knee jerk response (Figs. 3 and 4). The effects of reserpine on the polysynaptic reflexes were similar in both species, these reflexes being less

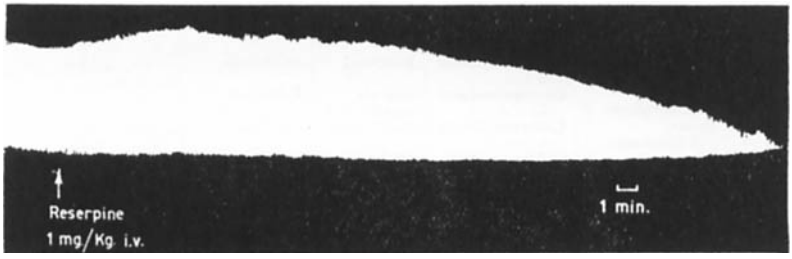

FIG. 3. Effect of reserpine on the patellar reflex of intact cat. 1 mg./kg. of reserpine induces an increase and then a disappearance of the knee jerk. Cat weighing 2·9 kg., anaesthetized with chloralose and urethane.

affected than the monosynaptic one (Fig. 4), being clearly inhibited only in 3 of 12 experiments. After the sectioning the spinal cord the knee jerk was not inhibited and in the cat usually became irregular and was even enhanced. In one rabbit and one cat the inhibition of the patellar reflex produced by reserpine in the intact animals was suppressed after a spinal section. However, this procedure produced in other animals a fall in the blood pressure such to induce us to disregard the results. Reserpine in decerebrate rabbits, in doses of 1–1·5 mg./kg., slightly inhibited the knee jerk reflex in one of 3 experiments. In this instance the section was intercollicular, while in the other two experiments the upper portion of the pons was involved. Blood pressure of intact animals is regularly and slowly lowered by reserpine. In spinal animals no effect was normally observed, though in some instances sudden falls of the blood pressure appeared. Concurrently with these pressure changes, both the patellar and linguo-mandibular reflexes may be temporarily depressed.

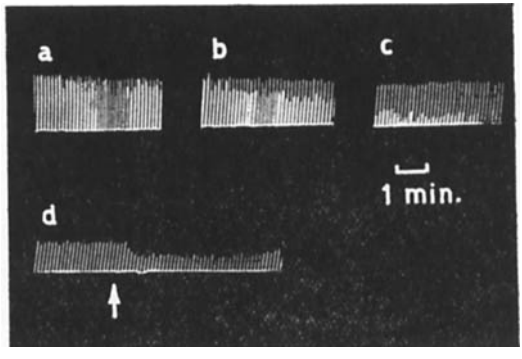

FIG. 4. Effects of reserpine on the patellar and the crossed extensor reflexes of intact animal. (*a*) Simultaneous recording of both patellar and crossed extensor reflexes. (*b*) 20 minutes after 0·5 mg./kg. of reserpine. The knee jerk appears to be inhibited, while the crossed extensor reflex is almost unaffected. (*c*) 30 minutes after reserpine. The knee jerk is markedly inhibited; the crossed extensor reflex is almost unaffected. (*d*) 60 minutes after reserpine. Mephenesin, 20 mg./kg. (at the arrow) produces an inhibition of the crossed extensor reflex. Cat weighing 2·2 kg., anaethetized with chloralose.

TABLE I

INDIVIDUAL RESULTS

Animal	Preparation	Drug mg./kg.	Linguo-mandibular reflex	Patellar reflex	Crossed extensor reflex	Depression of blood pressure in mm. Hg
Rabbit ..	Intact (chloralose)	Chlorpromazine 1	Inhibited	Inhibited	—	−30
Rabbit ..	Intact (chloralose)	Chlorpromazine 0·5	Inhibited	Inhibited	—	—
Rabbit ..	Intact (chloralose)	Chlorpromazine 1	Slightly inhibited	Inhibited	—	—
Rabbit ..	Intact (chloralose)	Chlorpromazine 1	Unaffected	Inhibited	—	−20
Rabbit ..	Intact (chloralose)	Chlorpromazine 1·5	Slightly inhibited	Inhibited	—	−15
Rabbit ..	Intact (chloralose + urethane)	Chlorpromazine 1·5	—	Inhibited	—	—
Rabbit ..	Intact (chloralose + urethane)	Chlorpromazine 0·5	—	Inhibited	—	—
Rabbit ..	Intact (chloralose + urethane)	Chlorpromazine 1	Slightly affected	Inhibited	—	—
Cat ..	Intact (chloralose)	Chlorpromazine 0·5	Inhibited	Inhibited	—	—
Cat ..	Intact (chloralose)	Chlorpromazine 0·5	Slightly affected	Inhibited	—	—
Cat ..	Intact (chloralose + urethane)	Chlorpromazine 1	Unaffected	Inhibited	—	−30
Rabbit ..	Spinal (C1)	Chlorpromazine 1	Inhibited	Unaffected	—	—
Rabbit ..	Spinal (L1)	Chlorpromazine 1	Slightly inhibited	Unaffected	—	—
Rabbit ..	Spinal (L1) (chloralose)	Chlorpromazine 1	—	Unaffected	—	—
Rabbit ..	Spinal section (L1) chloralose + urethane)	Chlorpromazine 1·5	—	Unaffected	—	−10
Rabbit ..	Intercollicular section	Chlorpromazine 1	—	Slightly inhibited	—	—
Rabbit ..	Prepontine section	Chlorpromazine 1	—	Unaffected	—	—
Rabbit ..	Pontine section	Chlorpromazine 1	—	Unaffected	—	—
Cat ..	Spinal (C1)	Chlorpromazine 1 + 1	Unaffected Inhibited	Unaffected Unaffected	—	—
Cat ..	Spinal section	Chlorpromazine 1·5	Slightly affected	Unaffected	—	—
Rabbit ..	Intact (chloralose)	Reserpine 0·3	Almost unaffected (irregular)	Slightly inhibited (irregular)	—	—
Rabbit ..	Intact (chloralose)	Reserpine 1 Mephenesin 20	Unaffected Inhibited	Inhibited Unaffected	—	—
Rabbit ..	Intact (chloralose)	Reserpine 0·4	—	Inhibited	—	—
Rabbit ..	Intact (chloralose)	Reserpine 1	Unaffected	Enhanced	—	−10
Rabbit ..	Intact (chloralose) Spinal section (L1)	Reserpine 0·4	— —	Inhibited Return	—	—
Rabbit ..	Intact (urethane)	Reserpine 0·5	Slightly inhibited	Inhibited	—	—
Rabbit ..	Intact (chloralose + urethane)	Reserpine 0·4	No effect	Inhibited	—	−10
Cat ..	Intact (chloralose)	Reserpine 1 + Reserpine 1	Almost unaffected	Almost unaffected	—	—
Cat ..	Intact (chloralose)	Reserpine 1	Inhibited	Enhanced and then inhibited	—	—
Cat ..	Intact (chloralose)	Reserpine 1·5	—	Inhibited 1 hour later	—	−30
Cat ..	Intact (chloralose)	Reserpine 1	Slightly inhibited	Enhanced, inhibited 1 hour later	—	−20

TABLE I—*continued*

Animal	Preparation	Drug mg./kg.	Linguo-mandibular reflex	Patellar reflex	Crossed extensor reflex	Depression of blood pressure in mm. Hg
Cat ..	Intact (chloralose)	Reserpine 1·2	Slightly inhibited	Inhibited 1 hour later	Slightly inhibited	—
Cat ..	Intact (chloralose)	Reserpine 1	—	Enhanced and then inhibited	Unaffected	—
Cat ..	Intact (chloralose) Section in L1	Reserpine 2	Slightly inhibited	Inhibited Return	—	−20
		Chlorpromazine 1		No effect		
Rabbit ..	Intercollicular section	Serpentine 1	—	Slightly inhibited	—	—
Rabbit ..	Pontine section	Serpentine 1·5	—	Unaffected	—	—
Rabbit ..	Pontine section	Serpentine 1	—	Unaffected	—	—
Cat ..	Spinal (C1)	Reserpine 2·5	Slightly affected	Unaffected	—	—
		Morphine 8	Inhibited	Inhibited	—	—
Cat ..	Spinal (C1)	Reserpine 1	Unaffected	Enhanced	—	−10
Rabbit ..	Intact (chloralose)	Promazine 2	Inhibited	Inhibited	—	—
Rabbit ..	Intact (chloralose + urethane)	Promazine 2	Unaffected	Inhibited	—	—
Rabbit ..	Intact (chloralose)	Promazine 1·5	Slightly inhibited	Inhibited	—	−20
Cat ..	Intact	Promazine 1	Unaffected	Inhibited	—	—
Rabbit ..	Spinal section (L1)	Promazine 2	Slightly inhibited	Unaffected	—	—
Rabbit ..	Prepontine section	Promazine 2	—	Almost unaffected	—	—
Rabbit ..	Pontine section	Promazine 2	—	Unaffected	—	—
Cat ..	Spinal section (C1)	Promazine 3	—	Unaffected	—	—
Rabbit ..	Intact (chloralose)	Hydroxyzine 10	—	Inhibited	—	—
Rabbit ..	Intact (chloralose)	Hydroxyzine 10	Slightly inhibited	Inhibited	—	—
Rabbit ..	Intact (chloralose + urethane)	Hydroxyzine 5+ Hydroxyzine 5	Unaffected Unaffected	Unaffected Inhibited	— —	— —
Cat ..	Intact (chloralose)	Hydroxyzine 10	Slightly inhibited	—	—	—
Rabbit ..	Prepontine section	Hydroxyzine 10	—	Slightly inhibited	—	—
Rabbit ..	Pontine section	Hydroxyzine 10	—	Unaffected	—	—
Cat ..	Spinal section (C1)	Hydroxyzine 10	—	Unaffected	—	—
Rabbit ..	Intact (chloralose + urethane)	Morphine 10	Slightly inhibited	Inhibited	—	—
Cat ..	Intact (chloralose + urethane)	Morphine 10	Inhibited	Inhibited	—	−20
Rabbit ..	Prepontine section	Morphine 10	—	Inhibited	—	—
Rabbit ..	Pontine section	Morphine 10	—	Inhibited	—	—
Cat ..	Spinal (C1)	Morphine 8	Slightly inhibited	Inhibited	—	−30
Rabbit ..	Intact (chloralose)	Diethazine 2	Inhibited	Slightly inhibited	—	—
Rabbit ..	Intact (chloralose urethane)	Diethazine 5	Inhibited	Inhibited	—	—
Rabbit ..	Pontine section	Diethazine 5	—	Slightly inhibited	—	—
Cat ..	Spinal section	Diethazine 10	Inhibited	Inhibited	—	—
Cat ..	Spinal (C1)	Diethazine 10	Inhibited	Inhibited	—	−15

Promazine acts on spinal reflexes as does chlorpromazine. Amounts of 1·5–2 mg./kg. decrease the knee jerk in the intact animals, while the linguo-mandibular reflex is inconsistently affected. After sectioning the

spino-cerebral axis at C1, L1, prepontine or pontine levels, effects on the knee jerk reflex disappear.

Hydroxyzine, in doses of 5–10 mg./kg., promptly suppresses the patellar reflex of the intact animals (Fig. 5), but only inconsistently depresses the linguo-mandibular reflex. In the spinal and decerebrate animals the patellar reflex is unaffected after the same dosage of hydroxyzine.

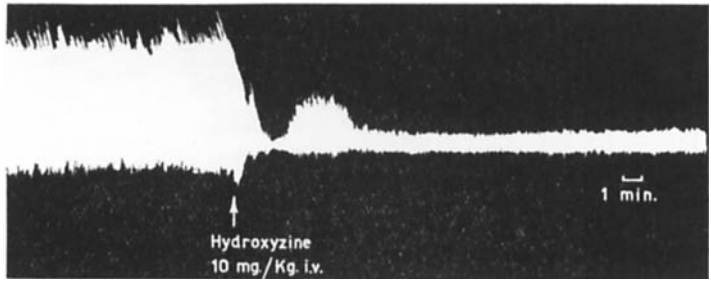

FIG. 5. Effects of hydroxyzine on the patellar reflex of intact animal. 10 mg./kg. of hydroxyzine results in an inhibition of the patellar reflex. Rabbit weighing 2·8 kg., anaesthetized with chloralose.

Morphine, in doses of 8 to 10 mg./kg., inhibits in intact, spinal and decerebrate animals, the polysynaptic reflex and to a minor extent the monosynaptic one (Fig. 6B and C).

Diethazine in doses of 2–5 mg./kg. was found to depress reflexes both in intact and in spinal animals, though in the latter case higher doses were required. The linguo-mandibular reflex is usually affected after 1–2 mg./kg.

DISCUSSION

Our results together with those obtained by other authors are summarised in Table II. These show that an intact connection between spinal cord and brain is essential for chlorpromazine, promazine, reserpine and hydroxyzine to produce inhibitory effects on spinal reflexes. The influence of the traumatic shock produced by the spinal sections on some patterns of reflex activity must not be disregarded, however. We did not observe any consistent change in the activity of morphine, diethazine and mephenesin on spinal reflex arcs before and after the sections of the spinal cord. The effects of anaesthesia cannot explain the peculiar behaviour of these drugs, as the experiments made on spinal animals previously anaesthetised with chloralose or urethane gave the same results. Haemodynamic depression may also be excluded, because it is known that polysynaptic arcs show a great sensitivity to changes in blood pressure and the effects on linguo-mandibular reflex were the same before and after the spinal sections.

Some findings indicate a possible role of the mesencephalon in these effects. Our experiments show that mesencephalic sections are critical, as small differences in the level of this section produce substantial changes in the action of these drugs. Schneider and others[1] did not find reserpine

to have any inhibitory effect in decerebrate animals, while Krivoy[2] has observed that the inhibitory action of reserpine and chlorpromazine is retained in this preparation. This may be explained by differences in the sections. On the other hand, many reported data demonstrate the presence of inhibitory and facilitatory centres in the reticular formation[10–13].

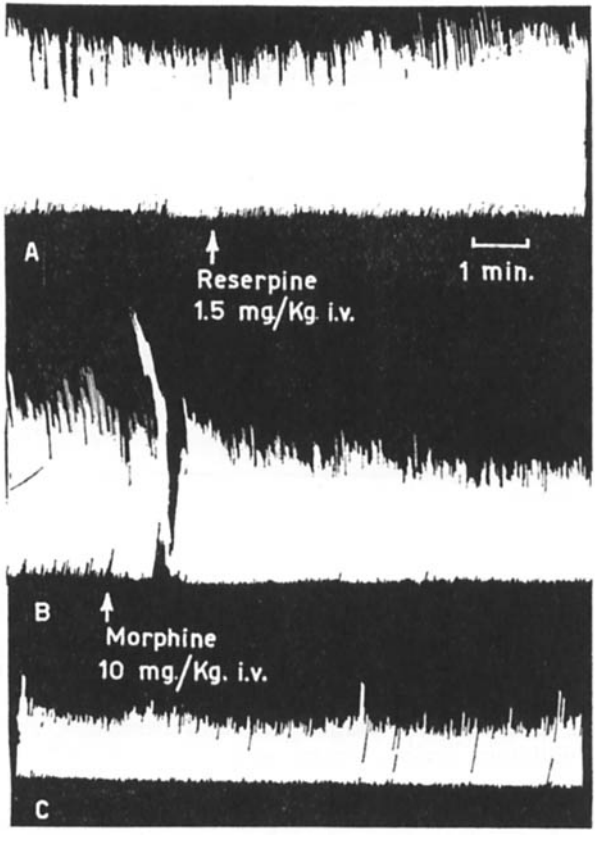

FIG. 6. Effects of reserpine and morphine on the knee jerk of a spinal animal.
(A) The patellar reflex is unaffected after 1·5 mg./kg. of reserpine. (B) 60 minutes after reserpine, the injection of 10 mg./kg. of morphine provokes an inhibition of the reflex response. (C) The inhibitory effect of morphine is evident 15 minutes after the injection. Cat weighing 2·5 kg., sectioned at C1 anaesthetized with ether.

Chlorpromazine, promazine, reserpine and hydroxyzine could act on these centres and two possible mechanisms may be considered. Firstly, the drugs might directly stimulate cerebral centres which exert an inhibitory action on motor reflexes. Secondly, the drugs might prevent some inhibitory cerebral centres from influencing opposing mechanisms.

Other drugs need the integrity of brain–spinal cord connections to inhibit spinal reflexes. Scopolamine was found by Teuchmann[14] to decrease the ipsilateral flexor reflex in the thalamic cat while no action in decerebrate and decapitate animals was found. De Maar[9], experimenting with cats the brain of which was sectioned at different levels, showed that an intact connection between diencephalon and spinal cord is necessary to demonstrate the actions of scopolamine and atropine on spinal reflexes

TABLE II

SUMMARY OF RESULTS

	Reflexes	Chlor-promazine	Promazine	Reserpine	Hydroxyzine	Morphine	Diethazine
Intact Animal	Linguo-mandibular	Incon-sistently inhibited	Incon-sistently inhibited	Incon-sistently inhibited	Slightly inhibited	Inhibited	Inhibited
	Monosynaptic	Inhibited (1 and 2)	Inhibited	Inhibited (1)	Inhibited (3)	Slightly inhibited (4)	Slightly inhibited
	Other polysynaptic	Inhibited (1 and 2)	—	Slightly inhibited (1)	—	Inhibited (4)	Inhibited (5)
Spinal Animal	Mono-synaptic	Unaffected (6 and 2)	Unaffected	Unaffected or en-hanced (7)	Unaffected (3)	Slightly inhibited (4)	Slightly inhibited
	Poly-synaptic	Unaffected (2, 6 and 8)	—	Unaffected (2)	—	Inhibited (4)	—

(1) See also Krivoy[2].
(2) „ „ Bein[3].
(3) „ „ Hutcheon and others[6].
(4) „ „ Wikler[7] and Takagi and others[8].
(5) „ „ De Maar[9].
(6) „ „ Preston[5].
(7) „ „ Schneider and others[1].
(8) Dasgupta and Werner[4] reported that the crossed extensor reflex was less inhibited in the spinal than in the decerebrated cats.

According to Bijlsma[15], orphenadrine (Disipal) inhibits the spinal reflexes through a cerebral mechanism, while other drugs used in paralysis agitans, such as diethazine, caramiphen and benzhexol, show a more widespread inhibitory action, similar to that displayed by mephenesin and morphine.

A second peculiar feature in the effects of chlorpromazine, promazine, reserpine and hydroxyzine appears to be the predominant inhibition of monosynaptic reflex activity. From a physiological point of view this finding is not completely surprising. In fact, King and others[12] have observed that the stimulation of certain centres of the bulbar reticular formation results in a facilitation of the linguo-mandibular reflex and in a simultaneous inhibition of the knee jerk. Alternatively, the stimulation of more rostral regions of the reticular formation, from the pons to the diencephalon, produces opposite effects. On the basis of these results one might assume the mono- and polysynaptic reflexes to be under the control of different cerebral structures, some of which would be affected by chlorpromazine, promazine, reserpine and hydroxyzine. We have been unable to find any mention of other drugs which predominantly inhibit monosynaptic reflexes. On the contrary, a selective inhibitory

action of polysynaptic reflexes has been considered to be a property common to many C.N.S. depressants[16]. Also, morphine and diethazine behave like other central depressant agents, and selectively affect polysynaptic arcs. This fact may be of some interest as morphine has been found to block the conditioned avoidance response of rats[17] as well as the secondary conditioned response[18], and in this resembles chlorpromazine and reserpine. However, morphine potentiates the stereotyped response induced by mescaline in mice, while promazine and chlorpromazine clearly abolish it[19]. The present study confirms that morphine has different and in some mechanisms opposite effects upon the regulation of spinal cord reflex activity to the tranquillising drugs examined.

On the other hand, diethazine, the chemical structure of which is strictly related to promazine, has been found to differ from the two other phenothiazines in its action on spinal reflexes. Diethazine is a drug of value in counteracting the symptoms of Parkinson's disease and it is supposed to act upon the reticular formation of the brain stem[20]. However, according to Balestrieri and Fadiga[21], chlorpromazine blocks the EEG arousal reaction which remains unchanged under diethazine treatment. This finding could be related to the differences of action on reflex activity, found by us, between chlorpromazine and diethazine, and perhaps may have some connection with the differences in therapeutic activity of the two drugs. In fact, it is known that diethazine does not possess the "tranquillising" activity of chlorpromazine and promazine.

The true significance of these findings is not clear, and it has not been possible to demonstrate any direct relation between the actions on reflex responses and the behavioural effects of the drugs investigated. We hope that from the present study a general picture of the actions of some psychotropic drugs on the spinal reflex activity may result which perhaps will have a practical importance for searching and investigating new drugs.

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