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CENTRAL EFFECTS OF HALOPERIDOL ON SOMATIC REFLEXES

BY

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Haloperidol and related compounds possess neuroleptic, analgesic, antiemetic and hypotensive properties (Janssen, 1962). It has been used as a depressant of the extrapyramidal system in diverse clinical conditions such as Parkinsonism, Huntington's chorea, delirium tremens, epilepsy, agitated psychoses and as an adjunct to anaesthesia (Delay, Pichot, Lemperiere & Elissalde, 1960; Pierre, 1961; Nodine, Bodi, Levy, Siegler, Slap, Mapp & Khorsandian, 1962; Brown, Horton & MacRae, 1963). The chemical structure of haloperidol closely resembles that of γ-aminobutyric acid and its central actions are similar to those of chlorpromazine (Janssen, 1961). γ-Aminobutyric acid has been reported to possess a nonspecific central depressant action on somatic reflexes (Bhargava & Srivastava, 1964) whereas chlorpromazine predominantly depresses monosynaptic reflex pathways (Krivoy, 1957). The present study was undertaken to investigate the effect of haloperidol on the central integration of monosynaptic and polysynaptic somatic reflexes both at spinal and at supraspinal levels in cats.

METHODS

Forty-four cats of either sex weighing between 2.8 and 4.0 kg were used. All surgical procedures were done during ether anaesthesia and subsequently the animals were maintained on light anaesthesia with α-chloralose (50 mg/kg, intravenously). All cats were vagotomized and maintained on artificial positive-pressure ventilation.

Drug solution was made by treating haloperidol with a few drops of 1.0% lactic acid and redistilled propylene glycol. The final volume was made up with warm 0.9% saline. Intrathecal injection was given through a hypodermic needle introduced at the lumbosacral articulation. Intracerebroventricular injection was made according to the technique of Feldberg & Sherwood (1954). For topical application of haloperidol to the medulla, a solution of 25 mg/ml. was prepared and a cotton pledget soaked in the drug was placed on the calamus scriptorius for 5 min. Cotton pledgets soaked in the vehicle (a few drops of 1.0% lactic acid, propylene glycol and 0.9% saline) were used as controls. In some experiments the blood pressure was recorded from a carotid artery by means of a mercury manometer.

The somatic reflexes were elicited 60 to 90 min after the administration of chloralose. The patellar monosynaptic reflex was elicited by tapping the patellar tendon, by means of an electromagnetic hammer, and recorded through a system of pulleys on a kymograph (Calma & Wright, 1947). Monosynaptic inhibition of the patellar reflex was elicited by stimulating the ipselateral sciatic nerve; the nerve of the opposite side was cut to avoid contralateral influences (Abdullan, Martin & Unna, 1960). Polysynaptic

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facilitation and inhibition of the patellar reflex were obtained by electrical stimulation of the contralateral sciatic nerve and brain-stem reticular formation (Henneman, Kaplan & Unna, 1949). A concentric needle electrode was used to stimulate the medullary reticular formation. The flexor reflex was recorded from the contractions of the tibialis anterior muscle produced by stimulation of the sciatic nerve distal to the origin of the nerve to the tibialis anterior muscle of the same side (Witkin, Spitaletta & Plummer, 1960). The polysynaptic linguomandibular reflex was activated by stimulating the root of the tongue according to the method of King & Unna (1954). All stimuli were derived from a Grass model S_4 electronic stimulator delivering rectangular pulses.

RESULTS

Studies in spinal transected (C7) cats

The patellar reflex was elicited in ten spinal cats. Intrathecal injection of haloperidol (0.25 to 1 mg) consistently depressed the patellar reflex and higher doses (3 to 5 mg) abolished it. However, doses above 3 mg were required to depress the patellar reflex facilitated by prior intrathecal administration of tetanus toxin (0.5 U) or tubocurarine (0.2 mg) or by intravenous injection of strychnine (0.02 mg/kg). Previous intrathecal injection of haloperidol (0.25 to 1 mg) prevented the facilitation of the patellar reflex by these agents. The inhibitory effect of haloperidol (0.25 to 1 mg) on the patellar reflex appeared within 15 min of intrathecal injection and the effect lasted for about 45 to 90 min depending upon the dose.

In three spinal cats the polysynaptic inhibition of the patellar reflex due to contralateral sciatic nerve stimulation (10 V, 120 shocks/sec for 10 sec) was elicited. Fig. 1 shows the result of a typical experiment. Intrathecal haloperidol (0.2 mg) reduced the patellar reflex at 20 min and the inhibition of the patellar reflex due to nerve stimulation was enhanced. Recovery occurred at 80 min.

The effects of haloperidol on the monosynaptic inhibition of the patellar reflex due to ipselateral sciatic nerve stimulation (0.5 V, 100 shocks/sec for 10 sec) were studied in four

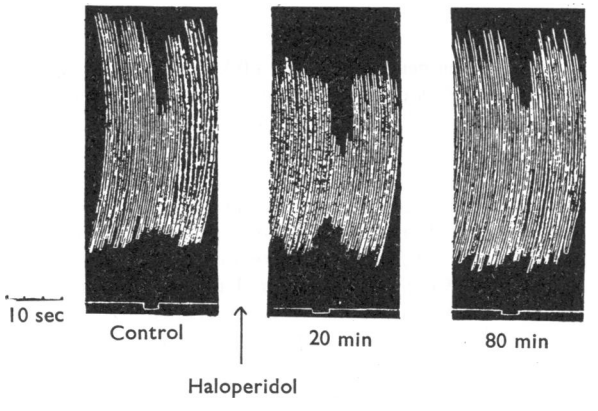

Fig. 1. Record of patellar tap response (PR), elicited every 1 sec, and the inhibitory effect of contralateral sciatic nerve stimulation (10 V, 120 shocks/sec, for 10 sec, at signal marks). Note that intrathecal haloperidol (0.2 mg at arrow) intensified the inhibition of the patellar response to nerve stimulation and the amplitude of the patellar response was also diminished. Complete recovery occurred at 80 min.

preparations. Intrathecal haloperidol (0.25 to 1.0 mg) consistently reduced the amplitude of the patellar reflex and prolonged the inhibition due to nerve stimulation. The inhibitory effect was observed within 20 min and recovery usually occurred at 90 min.

Polysynaptic facilitation of the patellar reflex was obtained in four cats by stimulation of the contralateral sciatic nerve (3 to 5 V, 120 shocks/sec for 10 sec). Fig. 2 shows the results of one such study. Intrathecal haloperidol (0.2 mg) reduced the facilitation of the

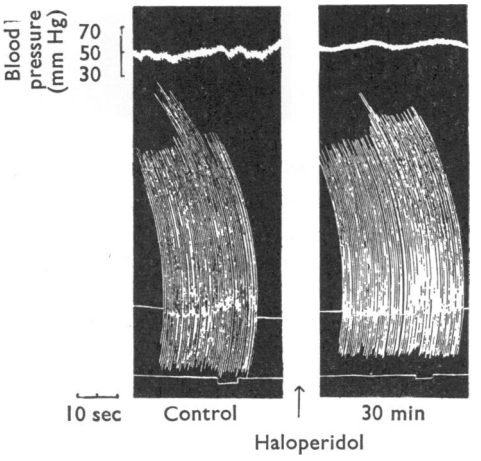

Fig. 2. Record of patellar tap response, every 1 sec, and the facilitation of the response to contralateral sciatic nerve stimulation (3 V, 120 shocks/sec, for 10 sec, at signal marks). Note that intrathecal haloperidol (0.2 mg, at arrow) antagonized the facilitation of the patellar response by nerve stimulation without affecting the amplitude of the patellar response. The blood pressure (upper tracing) remained unaffected.

patellar reflex due to nerve stimulation. The blood pressure (upper tracing) remained unchanged. Doses of haloperidol above 0.25 mg reduced the amplitude of the patellar reflex besides antagonizing the facilitation of the patellar reflex to nerve stimulation.

The effect of haloperidol on the tibialis anterior muscle (flexor reflex) response to nerve stimulation was studied in four cats. Intrathecal haloperidol (1 mg) gradually reduced the response of the tibialis anterior muscle to nerve stimulation (5 V, 1 shock/sec). Maximal depression of the flexor reflex was observed at about 30 min and recovery was seen at 90 min. The depressant effect of haloperidol on the flexor reflex was observed with doses above 0.25 mg.

Studies in intact cats

The effect of intracerebroventricular injection of haloperidol (0.01 to 0.05 mg) on the patellar reflex was studied in three cats. Each time haloperidol gradually depressed the patellar reflex. Recovery occurred in 100 to 130 min. Intraventricular injection (0.2 ml.) of the vehicle did not affect the patellar reflex.

Polysynaptic facilitation of the patellar reflex was elicited in three cats by stimulation of the brain-stem reticular formation (3 to 5 V, 100 shocks/sec for 5 sec). Fig. 3 shows the

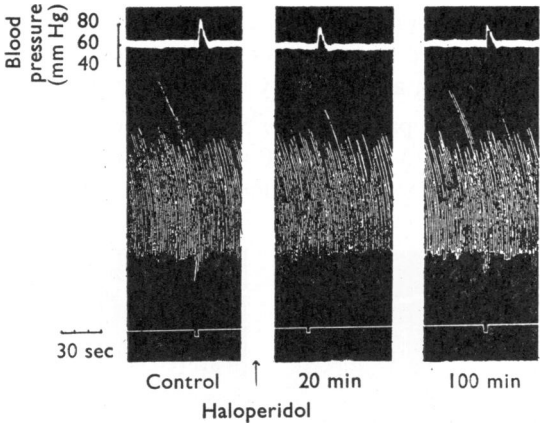

Fig. 3. Effect of haloperidol on polysynaptic facilitation of patellar reflex (lower trace) and pressor responses (upper trace) induced by electrical stimulation (4 V, 100 shocks/sec for 5 sec, at signal marks) of the brain stem reticular formation. Haloperidol (25 mg/ml., at arrow) was applied for 5 min in a cotton pledget on calamus scriptorius. Note the depression of the patellar facilitation at 20 min and slight inhibition of pressor response. Recovery had occurred at 100 min.

results of one such experiment. The electrode placement was done by means of a stereotaxic instrument (co-ordinates: anterior 12 to posterior 6 mm, lateral 4 to 5 mm and vertical −1 to 5 mm; see also Henneman *et al.*, 1949). The control panel shows facilitation of the patellar reflex by stimulation (4 V, 100 shocks/sec for 5 sec) of the medullary reticular formation. The reticular stimulation also elicited a pressor response. Topical application of haloperidol (25 mg in 1 ml. for 5 min) on the exposed calamus scriptorius inhibited the facilitation of the patellar reflex to reticular stimulation. Recovery of this depressant action of haloperidol was observed at 100 min. Topical application of higher concentrations of haloperidol (50 to 100 mg in 1 ml.) reduced the amplitude of the patellar reflex and the pressor response to reticular stimulation.

Polysynaptic inhibition of the patellar reflex due to stimulation of the brain-stem reticular formation (0.4 to 0.6 V, 100 shocks/sec for 5 sec) was studied in four cats. The electrode placement was done according to the following stereotaxic co-ordinates: posterior 8 to 10 mm, lateral 0 to 2 mm and vertical −5 to −8 mm. Topical application of haloperidol (25 mg in 1 ml. for 5 min) on the calamus scriptorius enhanced the inhibition of the patellar reflex to reticular stimulation at 30 min (Fig. 4). Application of higher concentrations of haloperidol (50 to 100 mg in 1 ml.) reduced the amplitude of the patellar response, and the depressor response to reticular stimulation was also enhanced.

The effect of intracerebroventricular injection of haloperidol (0.01 and 0.02 mg) was observed on the polysynaptic linguomandibular reflex in seven cats. Haloperidol consistently reduced the amplitude of the reflex within 5 min and recovery occurred in about 100 min. Similarly intravenous administration of haloperidol (0.1 to 2.0 mg/kg) inhibited the linguomandibular reflex in two cats. Doses of haloperidol lower than 0.01 mg/kg were ineffective.

In another preparation the effects of *intravenous* haloperidol were observed simultaneously on the linguomandibular reflex and the patellar reflex. Fig. 5 shows the results of such a

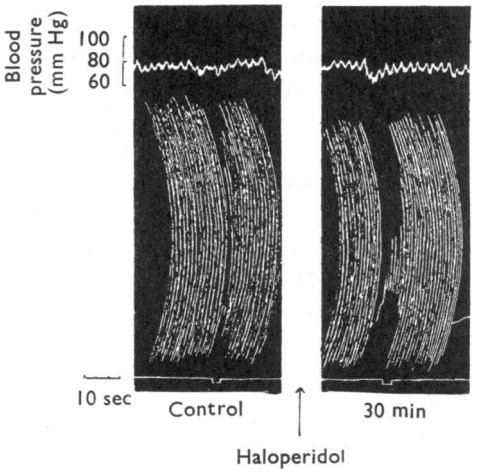

Fig. 4. Record of patellar tap response (lower tracing) every 2 sec, and its inhibition by stereotaxic stimulation of the brain stem reticular formation (0.5 V, 100 shocks/sec for 15 sec, at the signal marks). Topical application of haloperidol (25 mg in 1 ml., at the arrow) was for 5 min on the calamus scriptorius. Note the increased inhibition of the patellar response to reticular stimulation at 30 min. The vasodepressor response to reticular stimulation (upper tracing) was also larger.

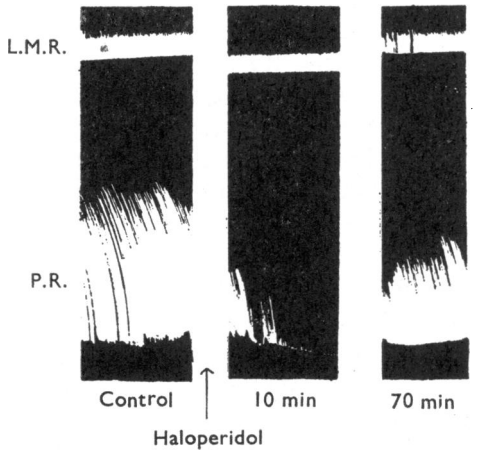

Fig. 5. Effect of haloperidol on the linguomandibular (polysynaptic) reflex (L.M.R., upper trace) induced by electrical stimulation (3 V, 1 shock/sec) of the root of tongue, and the patellar (monosynaptic) reflex (PR, lower trace) induced by patellar tap once every 10 sec. Intravenous haloperidol (4 mg/kg, at arrow), at 10 min, depressed the linguomandibular reflex and the patellar response was abolished. Recovery was seen at 70 min.

study. An intravenous injection of haloperidol (4 mg/kg) depressed the linguomandibular reflex, and the patellar reflex was completely blocked at 10 min. Thus, the monosynaptic reflex integrated at the spinal level was more depressed than the polysynaptic reflex integrated at the brain-stem level. Recovery of the reflexes was apparent at 70 min.

DISCUSSION

The effects of haloperidol on the central integration of somatic reflexes observed in the present study were similar to those of γ-aminobutyric acid reported earlier (Bhargava & Srivastava, 1964). Intrathecal injection of haloperidol depressed the monosynaptic patellar reflex and the polysynaptic facilitation of the patellar reflex due to contralateral sciatic nerve stimulation. The monosynaptic inhibition of patellar reflex due to ipselateral sciatic nerve stimulation and the polysynaptic inhibition of the patellar reflex induced by contralateral sciatic nerve stimulation were augmented. Similar depressant action on the patellar reflex was observed upon intracerebroventricular injection of haloperidol. The polysynaptic linguomandibular reflex was similarly depressed.

The facilitation of the patellar reflex induced by brain-stem reticular stimulation was depressed and the inhibition of the patellar reflex induced by stimulation of another region was enhanced by topical application of haloperidol. Thus, haloperidol seems to inhibit synapses at all levels of the neuraxis. The facilitation as well as the inhibition of the patellar reflex induced by different stimulation procedures was more amenable to drug action than was the patellar reflex itself.

There does not seem to be a barrier against the penetration of haloperidol into the central nervous system since the effects of intravenous administration were similar to those of intrathecal, intracerebroventricular or topical application. Unlike most central nervous depressants, haloperidol inhibited the monosynaptic patellar reflex more effectively than the polysynaptic linguomandibular reflex. This could be due either to a greater specificity of the agent on monosynaptic systems or to a greater concentration of the drug in the spinal cord. These actions are similar to the effects of chlorpromazine on these reflexes and are different from those of mephenesin (Silvestrini & Maffii, 1959). Inhibition of the monosynaptic reflex is a property of the major tranquillizers, chlorpromazine and reserpine (Krivoy, 1957). For want of a clear understanding of the transmission at the central synapses involved, the selective action of haloperidol on the monosynaptic reflexes cannot be explained.

SUMMARY

1. The monosynaptic extensor reflex induced by patellar tap was inhibited by haloperidol administered intravenously, intrathecally or intracerebroventricularly.

2. The polysynaptic facilitation of the patellar reflex induced by stimulation of the contralateral sciatic nerve or brain-stem reticular formation was depressed, and the inhibition of the patellar reflex induced by stimulation of the sciatic nerve or the brain-stem was enhanced by haloperidol. The monosynaptic inhibition of the patellar reflex induced by ipselateral sciatic nerve stimulation was also enhanced.

3. The monosynaptic or polysynaptic facilitation as well as the inhibition of the patellar reflex induced by different stimulation procedures were more susceptible to drug action than the patellar reflex itself.

4. The tibialis anterior flexor reflex and the linguomandibular reflex were depressed by haloperidol.

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