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ACTION OF NICOTINE ON THE SPINAL CORD

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In previous papers [Schweitzer & Wright, 1937*b*, *c*, *d*, *e*, 1938] we examined the action of various autonomic drugs (adrenaline, acetylcholine and related substances, eserine and other anticholinesterases) on the central nervous system. In extension of this work we have studied the action of nicotine on the central nervous system, using the knee jerk as a typical spinal reflex. Dixon in his review in Heffter's *Handbuch* [1924] states that the main action of nicotine on the spinal cord is to produce convulsions. Langley & Dickinson [1890] give a detailed account of the action of nicotine in the frog, which is in agreement with the evidence of previous observers. There is initial excitement, followed by spasms, tonic rigidity and catalepsy. Finally the skeletal muscles become flaccid and reflex activity disappears. Langley [1901] noted that when a 1 % solution of nicotine is painted on to the spinal cord of the skate a violent discharge of impulses from the treated region takes place.

In the mammal, according to v. Praag [1855], Krocker [1868] and Truhart [1869], nicotine produces preliminary excitement, clonic spasms and twitchings of various muscles. Convulsions and opisthotonus were also noted. In the cat there is rigidity of the forelimbs (which is abolished by section of the peripheral nerves) and twitching may develop in the ears. Langley & Dickinson [1890] state that all these phenomena may be seen at times in anaesthetized animals, but to a lesser degree. Other observations, however, suggest that the excitatory actions of nicotine are not always easily evoked. Thus, Langley [1901] states that "in anaesthetized animals I have not found appreciable effects on applying nicotine locally to the spinal cord". On injecting 1 mg. of nicotine in 0·1 % solution peripherally into the 3rd lumbar artery of a deeply anaesthetized animal there was intense stimulation of sympathetic ganglia, but no muscular movements. In the mammal, Langley &

Dickinson [1890] "did not find any great difference between the time of disappearance of reflex contraction and muscular contraction produced by stimulating the motor nerve. As long as stimulation of the uncut sciatic nerve causes contraction of the leg on the side stimulated, it causes also reflex movements." Langley [1918–19] injected 2–5 mg. of strychnine into the anaesthetized cat. The subsequent injection of nicotine in doses up to 100 mg. in no case prevented clonic contractions in a leg with ligatured vessels. He concludes, therefore, "it follows that nicotine has no specific paralyzing action either on the anterior cornual cells or on the commissural cells on which strychnine is generally supposed to act". Sollmann [1937] summarizes the central action of nicotine by stating that it consists of stimulation followed by depression of the whole cerebrospinal axis from above downwards. Finally, it may be added that nicotine in strengths of 0·1–1 % directly applied to the spinal ganglia of mammals produces no stimulating or paralyzing action [Langley, 1901].

Methods

Cats were used under chloralose anaesthesia (0·065–0·08 g. per kg. body weight). In a number of experiments decerebrate animals were used after 1 hr. or more had been allowed to elapse for the effects of the initial ether-chloroform anaesthesia to wear off. The knee jerk on one side and the response of the gastrocnemius muscle of the contralateral side to submaximal break shocks applied to its motor nerve were recorded, using our customary technique, which has been fully described in previous communications [Schweitzer & Wright, 1937*a–e*]. We used the "ischaemic hindlimb technique" to determine the extent to which nicotine produced its effect by an action on the central nervous system or on peripheral structures. In a number of experiments the carotid sinuses were denervated and the vagi cut. The injections of the drug were made into the jugular vein.

Results

In the cat under chloralose anaesthesia, intravenous injection of nicotine depresses or abolishes the knee jerk (Fig. 1). The dose required to produce this effect varies considerably with the sensitivity of the preparation. The minimal dose which has produced a depression of the knee jerk is, in our experience, about 5μg. in animals weighing 3–4 kg. We have never noticed any increase in the knee jerk at any stage of the response, or with any size of dose. Doses which are too small to produce inhibition have no effect at all on the reflex. In some experiments we have

elicited the knee jerk at intervals of 1 per sec., instead of the usual one in 10 sec., but under these conditions also we failed to demonstrate any initial phase of stimulation (Fig. 2).

The latent period of the response is very short. In some experiments the inhibition sets in within 5 sec. of the moment of injection. The knee

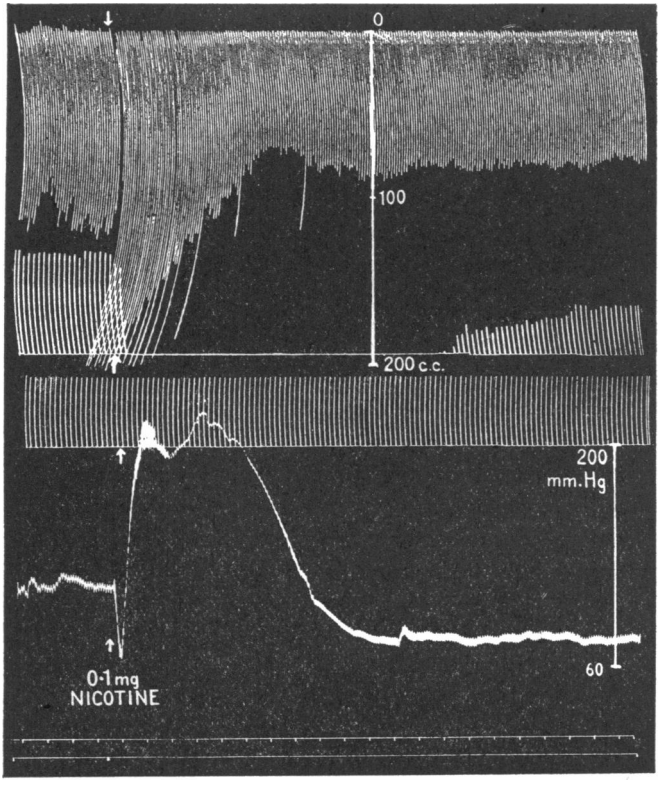

Fig. 1. Cat, chloralose. Records from above downwards are: quantitative record of breathing (Wright's method [1934], inspiration downwards), knee jerk (right side) every 5 sec., contraction of gastrocnemius (left side) stimulated through its motor nerve every 5 sec., carotid blood pressure, time in 30 sec., signal line. Inject 0·1 mg. nicotine into jugular vein.

jerk declines at a rate which varies with the dose. The maximal depression may be reached at once, or develop more slowly over periods of 10–60 sec. The duration of the effect varies widely, but may persist for many minutes, e.g. 5–10 min. or longer. Sometimes no recovery takes place in half an hour or more, or if recovery takes place, it is gradual and incom-

plete even up to 1 hr. or longer. We have analysed the mechanisms of production of these effects.

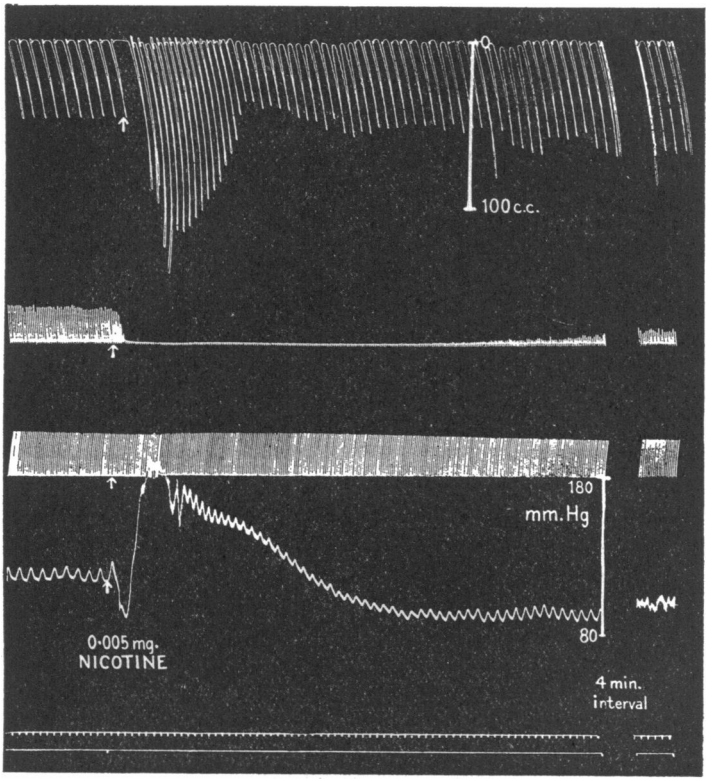

Fig. 2. Cat, chloralose. Records from above downwards are: respiration, knee jerk, nerve muscle preparation and blood pressure as in Fig. 1, knee jerk and gastrocnemius contractions elicited every sec., time in 5 sec. Inject 0·005 mg. nicotine into jugular vein. Pure depression of knee jerk.

Relation to blood pressure

Nicotine produces a rise of blood pressure of varying extent and duration, depending upon the dose used. This rise is not uncommonly preceded by a short initial fall of pressure. The effect on the knee jerk may come on just as rapidly whether the rise of blood pressure is preceded by an initial fall or not. We have previously [Schweitzer & Wright, 1937*a*, *b*] studied the effects of variations in blood pressure on the knee jerk, and have shown that a rise of blood pressure produced by

occlusion of the carotid arteries or the injection of tyramine or pituitrin has no effect on the knee jerk. A fall of blood pressure only produces an effect when it is about 100 mm. in extent or when it lowers the pressure to about 40 mm. The effect is then one of stimulation. In the light of these observations it is most improbable that the small initial fall or the greater subsequent rise of pressure is responsible for the knee-jerk changes observed. Furthermore, the recovery of the knee jerk bears no relationship to the course of the blood-pressure curve; the knee jerk may remain absent when the blood pressure has returned to or fallen below its pre-injection level. In some experiments, small doses of nicotine which altered the blood pressure only very slightly produced the usual depression of the knee jerk.

Relation to adrenaline secretion

We have previously shown [Schweitzer & Wright, 1937*b*] that the intravenous injection of adrenaline in doses of 0·2 mg. or upwards may depress or abolish the knee jerk. It is well known that nicotine stimulates the secretion of adrenaline from the adrenal medulla [Cannon *et al.* 1911–12; Gley, 1914], and it was thought possible, therefore, that the adrenaline so liberated might be responsible, in part at least, for the results noted. In a series of animals the adrenal veins were ligated or the glands extirpated. The subsequent injection of nicotine into these animals produced a characteristic depression of the knee jerk.

Relation to respiratory changes

In the doses employed, nicotine produces characteristic respiratory changes, namely a very brief initial apnoea, followed by an intense stimulation (consisting of an increase in rate or depth, or both) and a gradual return to normal. In the decerebrate preparation the stimulation is more persistent and may last for 10 or more minutes. In previous experiments [Schweitzer & Wright, 1937*a*] we have studied the effects of alterations in pulmonary ventilation on the knee jerk. Severe over-ventilation sufficient to produce a considerable reduction in the CO_2 tension of the blood did not affect the knee jerk. The depression in the knee jerk following an injection of nicotine cannot, therefore, be reasonably attributed to the alterations in breathing.

Role of vaso-sensory nerves

In a number of experiments we have denervated the carotid sinuses and divided the vagi prior to the injection of nicotine. The usual changes in the knee jerk were obtained under these circumstances (Fig. 3). These

experiments exclude the possibility that nicotine produces its effects reflexly, either *via* the pressor-receptors or the chemo-receptors in the carotid sinus region and the aortic arch. They provide additional evidence that the knee-jerk changes are independent of alterations in the breathing.

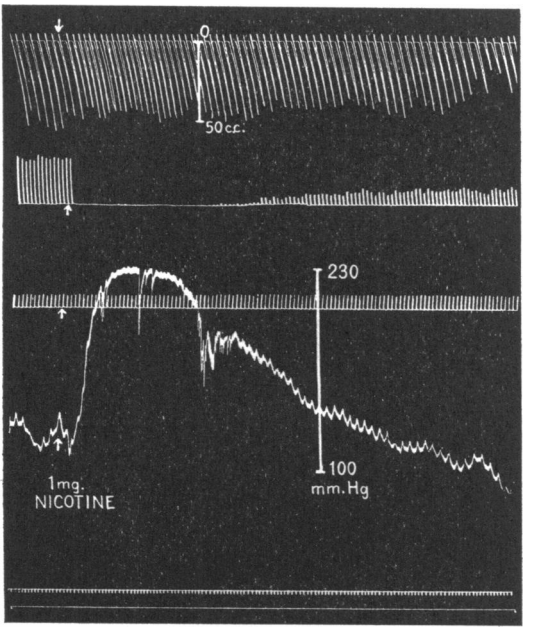

Fig. 3. Cat, chloralose. Both carotid sinuses denervated and both vagi cut. Records from above downwards are: respiration, knee jerk, nerve muscle preparation and blood pressure as in Fig. 1, knee jerk and gastrocnemius contractions elicited every 6 sec., time in 5 sec. Inject into jugular vein 1 mg. nicotine.

In the denervated preparation, nicotine produces no stimulation, or only slight stimulation, of breathing [Wright, 1935], but the effect on the knee jerk is still observed.

Action on skeletal muscle

In many of our experiments we have recorded the effects of stimulation of the gastrocnemius through its motor nerve on one side, at the same time as we elicited the knee jerk on the other side. Doses of nicotine that may abolish the knee jerk produce no effect whatever on the response to motor-nerve stimulation, even when applied at a frequency of 1 per sec. G. Briscoe informs us that doses of nicotine of 0·1–1 mg. have no effect on the nerve-muscle responses, not only when low, but also when high

rates of stimulation (60 per sec. and over) are employed. In her experiments also, though there was no change in the peripheral response, the knee jerk was abolished. The changes in the knee jerk observed are, therefore, not due to alterations in the response of the quadriceps muscle itself.

We have confirmed this conclusion, however, by the use of the ischaemic preparation previously described (Fig. 4). In many experiments,

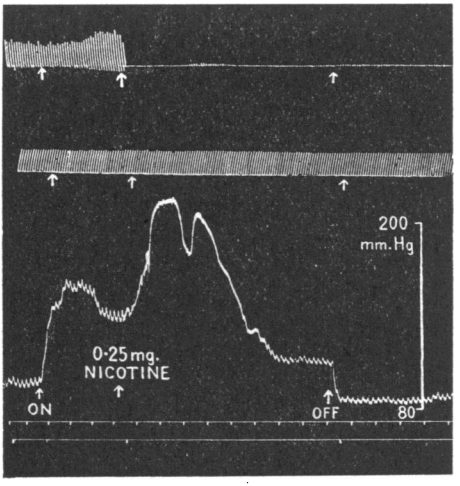

Fig. 4. Cat, chloralose. "Ischaemic preparation." Records from above downwards are: knee jerk (right side) and contraction of gastrocnemius (left side) stimulated through its motor nerve every 5 sec., carotid blood pressure, time in 30 sec., signal line. At "On" clamp abdominal aorta and inferior vena cava. At arrow inject 0·25 mg. nicotine into jugular vein. At "Off" release clamps.

after the blood supply to the hindlimb had been completely cut off, the intravenous injection of nicotine depressed or abolished the knee jerk. Under the conditions of the experiment the drug could only produce its effects by an action on the central nervous system, or on the peripheral nerves. The second possibility, however, is excluded by the fact that very much larger doses have no action on the nerve-muscle preparation, and therefore cannot be depressing conduction in the motor nerves.

Observations on the decerebrate animal

A certain number of experiments were carried out in decerebrate preparations, which have proved more resistant to the inhibitory action of nicotine than animals under chloralose anaesthesia. This is in no way

surprising, as it can be readily supposed that the presence of an anaesthetic facilitates the depressant action of nicotine. In the decerebrate animal (Fig. 5) the depression comes on more gradually, larger doses of the drug have to be employed, and recovery is more rapid and more complete.

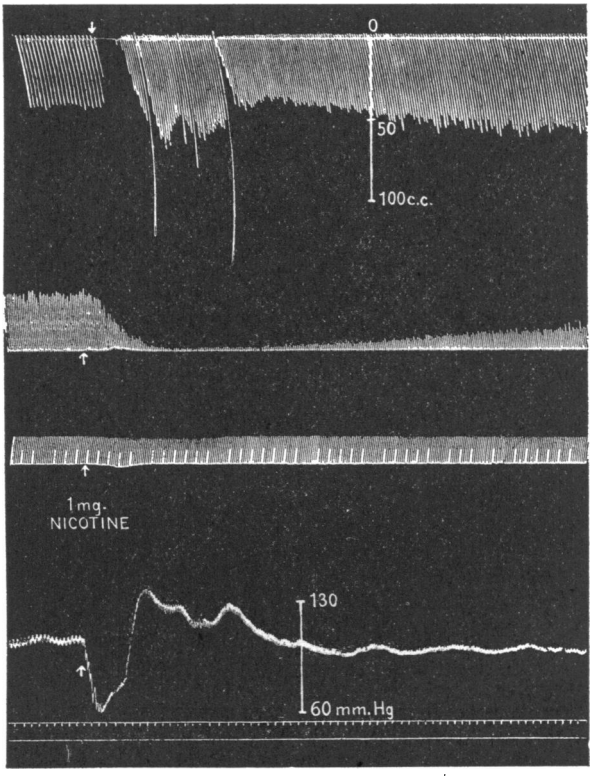

Fig. 5. Decerebrate cat. Records from above downwards are: respiration, knee jerk, nerve muscle preparation and blood pressure as in Fig. 1, knee jerk and gastrocnemius contractions elicited every 1 sec., time in 5 sec.

In none of these animals was stimulation of the knee jerk noted. Special attention was paid to this point in view of Langley's [1901] statement that the excitatory effects of nicotine are depressed by anaesthesia.

In decerebrate animals made spinal by transection of the cord in the lower thoracic regions, the usual effects on the knee jerk were observed. Again, no stimulation was noted.

Anti-strychnine action of nicotine

Contrary to the results of Langley [1918–19], we were able to demonstrate that nicotine exerts an anti-strychnine action. As with all drug antagonisms, the relative doses of the two substances must be

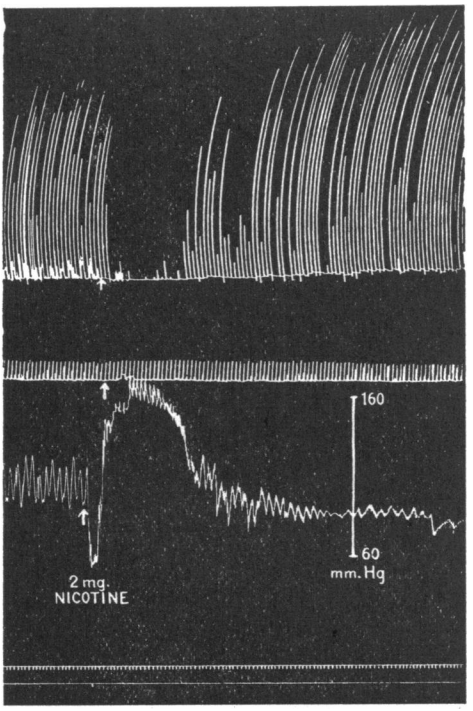

Fig. 6. Cat, chloralose. Knee jerk (right side), contractions of gastrocnemius (left side) stimulated through its motor nerve every 5 sec., carotid blood pressure, time in 5 sec., signal. 0·1 mg. strychnine was previously injected four times in succession into the jugular vein, leading to an increase in the knee jerk and onset of convulsions. At arrow: inject 2 mg. nicotine into the jugular vein. Convulsions reappear and knee jerk temporarily abolished.

carefully adjusted. Our practice has been to inject small doses of strychnine, e.g. 0·1 mg., and repeat the dose until the knee jerk was markedly enhanced, and spontaneous convulsions set in. At this stage large doses of nicotine, e.g. of the order of 2 mg., may abolish both the knee jerk and the convulsions (Fig. 6). The effect, however, is usually short-lived. Recovery takes place much more rapidly than in unstrychninized animals, and the convulsions may subsequently return.

Discussion

Our experiments show that nicotine exerts a depressant action on spinal reflexes in the cat. In view of the contradictory statements in the older literature and the known initial excitatory action of nicotine on autonomic ganglia, we paid special attention to possible excitatory effects of the drug on the central nervous system. We were unable, however, using the patellar reflex as a typical spinal reflex, with the dose of nicotine employed (1μg.–2 mg./kg. body weight) to demonstrate any excitatory effect of the drug on the knee jerk, nor did we notice any other signs of heightened central excitation, such as convulsions. Even very transient excitatory changes in the spinal reflexes occurring within at least 1 sec. of injection would have been recorded in the series of experiments in which the knee jerk was elicited at intervals of 1 sec. The possibility that any excitatory effect of nicotine on the central nervous system was suppressed by the anaesthetic used was tested in experiments on decerebrate preparations, in some of which the spinal cord was subsequently divided in the lower thoracic region. No sign of central excitation was observed in any of these experiments. It is not surprising that decerebrate cats showed a greater resistance to the depressant effect of the drug than animals under chloralose anaesthesia, as in the former preparation there is increased muscular tone due to a greater discharge from the anterior horn cells.

Further evidence for the central depressant action of nicotine was obtained by the experiments in which nicotine was pitted against heightened excitability of the spinal cord produced by a preceding injection of strychnine. As already pointed out, drug antagonisms can only be successfully demonstrated when suitable relative doses are employed. In our experience, nicotine depresses or even abolishes the increased patellar reflex and the convulsions induced by intravenous injections of strychnine.

The role of the carotid sinus and aortic nerves was carefully studied. It is known that increased pressure within the carotid sinuses may inhibit the knee jerk and decrease muscular tone in dogs (full discussion, cf. Schweitzer, 1937). Furthermore, central vagus stimulation in the cat decreases the patellar reflex and may inhibit strychnine convulsions [Schweitzer & Wright, 1937*a*, *e*; Schweitzer, 1937]. The increase of arterial blood pressure following an intravenous injection of nicotine might, therefore, be responsible for the phenomena observed. Our experiments on animals in which the pressor-receptor and chemo-receptor mechanisms of the carotid sinus region and the aortic arch were elimi-

nated show that the depression or abolition of the knee jerk by nicotine is not exclusively brought about reflexly *via* the vaso-sensory nerves.

We conclude that nicotine depresses spinal reflexes and counteracts the heightened reflex activity and the convulsions induced by strychnine by a direct action on the spinal cord. This conclusion is partly supported by recent work of Therman [1938] and Barron & Matthews [1938]. Therman reported a paralyzing effect of nicotine on the retinal action potentials of the excised frog's eye, consisting mainly of a decrease and slowing down of the reactions. Barron & Matthews observed that nicotine abolished in frogs the slow dorsal root potentials which probably originate in the grey matter of the spinal cord. de Kleyn [1938] studied the effects of acetylcholine and nicotine on vestibular responses. If a solution of either drug is applied to the orbital contents in which the ocular muscles had been dissected free, a distinct retardation of the frequency of the nystagmus occurs, not only on the affected side, but also in the opposite eye. In view of the fact that intravenous injection of the drugs did not influence the nystagmus, de Kleyn concluded that the drug could not have acted on the central nervous system. It is difficult, however, to see how any peripheral action could have produced the effects noted, especially in the other eye, and it is more probable that the drugs were absorbed by some non-vascular route into the central nervous system.

Summary and conclusions

1. Nicotine depresses or abolishes the knee jerk in cats under chloralose anaesthesia, and in the decerebrate or spinal preparation. It also depresses or abolishes strychnine convulsions. Excitatory effects have not been observed, even with small doses (0·005 mg.).

2. This action is independent of changes in respiration and blood pressure. It is still obtained after denervation of both carotid sinuses and section of both vagi, and exclusion of both adrenal glands.

3. The depressant effect of nicotine on the knee jerk is not due to changes in the response of the peripheral muscles to motor nerve stimulation. It is obtained in "ischaemic preparations" in which the drug does not reach the hindlimbs.

4. It is concluded that nicotine inhibits spinal reflexes by a direct action on the spinal cord.

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Note added in proof. Experiments reported by B. Libet & R. Gerard, 1938, *Proc. Soc. exp. Biol., N.Y.*, **38**, 886 (which appeared while this paper was passing through the Press), provide independent testimony in support of the central depressant action of nicotine in the frog and cat. In "ischaemic" experiments in cats intravenous injection of nicotine abolished crossed and uncrossed spinal reflexes. Local application of 2·5 mg./kg. in the cat blocked tactile action potentials in the thalamus.