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ANTIDIURETIC EFFECT OF NICOTINE AND ITS IMPLICATIONS*

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Antidiuretic Effect of Acetylcholine

Anyone who is prepared to investigate the effects of tobacco smoking lays himself open to the suspicion that he may be a crank and is probably a killjoy. Nevertheless, it must be admitted that the habit of smoking tobacco is widespread, and that the pharmacologist ought to pay some attention to the effects of a drug which is used in greater amount than any other.

Our interest in nicotine began as a consequence of observations made in Edinburgh by Dr. Mary Pickford (1939). She observed that acetylcholine possessed an antidiuretic action in dogs. We know acetylcholine to be the substance which transmits the nervous impulses passing along the vagus to the organs it innervates, and we also know acetylcholine to be a substance liberated in autonomic ganglia, where it transmits the impulse from the pre-ganglionic to the post-ganglionic fibre. The actions which acetylcholine exerts at vagal nerve endings were described by Dale as resembling the actions of muscarine, while those exerted at autonomic ganglia were said to resemble the actions of nicotine. The two kinds of action can be distinguished, as the muscarine actions are abolished by atropine, and in animals under atropine only nicotine-like effects are seen.

Dr. Pickford observed the antidiuretic action by giving dogs water by mouth, and, having also given atropine, she injected acetylcholine intravenously when diuresis was at its height. The antidiuretic action was seen at once and lasted for nearly an hour. She proved that it was due to liberation of the hormone of the posterior lobe of the pituitary, by removing almost the whole of this lobe in some of her animals; in these, only a small fraction of the antidiuretic response to acetylcholine remained. Thus she showed that one of the nicotine-like properties of acetylcholine was to liberate the antidiuretic hormone of the posterior lobe.

Later Dr. Pickford (1947) was able to demonstrate that the site of action of the acetylcholine was the supraoptic nucleus from which nerve fibres pass to the posterior lobe. She accomplished this by making injections of small amounts of acetylcholine (2–40 μg.) directly into the supraoptic nucleus; these caused the antidiuretic action.

The Action of Nicotine

To test nicotine to see if it exerted a similar action was then an obvious step, which we took in the Oxford laboratory (Burn, Truelove, and Burn, 1945). We made observations in groups of rats and showed that nicotine exerted an antidiuretic effect, but failed to do so if rats were used from which the pituitary body was first removed. The amount of nicotine needed to produce the antidiuretic action was large, being 0.16 mg. per 100 g. rat. We had therefore established a point of some slight academic interest.

In view of the dose of nicotine required in the rat it seemed scarcely worth while to test the effect of nicotine in man, and we were greatly surprised to discover that the smoking of one or more cigarettes, according to the sensitivity of the subject, caused an inhibition of the diuresis which followed the drinking of 1 litre of water, and that the antidiuretic action lasted for one, two, or even three hours.

The observations were made on subjects each of whom emptied his bladder at 15-minute intervals. When it was observed that the excretion was regular and less than 25 ml., the subject drank 1 litre. By 45 minutes later the excretion of water had reached perhaps 70 ml. per 15 minutes, and at that point he began to smoke, and was asked to inhale as much as he felt inclined. The inhibition occurred within 10–15 minutes, and in those subjects in whom it was prolonged it was accompanied by toxic symptoms such as pallor, sweating, dizziness, nausea, and sometimes vomiting. These were, however, of short duration, and the period of inhibition outlasted them by two to three hours. When the period of inhibition was shorter, as after smoking one cigarette, it was rare to observe any toxic effects other than transient dizziness and pallor.

Intravenous Injection of Nicotine

To establish that the effect of smoking was due to the nicotine inhaled, we carried out experiments in which the subject did not smoke, but received an intravenous injection of nicotine acid tartrate. We observed that amounts corresponding to 0.33 to 1 mg. of nicotine (as free base) caused an antidiuretic action resembling in duration that due to the smoking of one to three cigarettes. Ling and Wynn Parry (1949) have estimated as a result of a careful study that the amount of nicotine entering the mouth of a smoker from one cigarette is about 1 mg. If it is assumed that about one-third of this is absorbed into the blood stream when the subject

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inhales, we then have fair agreement between the antidiuretic effect of nicotine injected intravenously and of nicotine inhaled through the lungs.

The antidiuretic action of nicotine given intravenously has been studied by Garrod and Cates (1950) in diabetes insipidus; they found that doses effective in normal subjects or those with functional polydipsia were ineffective in diabetes insipidus, and for patients suffering from this disease much larger amounts were required to produce an antidiuretic action.

Mode of Action of Nicotine in Man

The mode of action of nicotine in man is, for the reasons which have already been given, likely to be similar to that of acetylcholine in the dog—that is to say, to be an action due to stimulation of the supraoptic nucleus with resulting liberation of the antidiuretic hormone from the pituitary posterior lobe. Taylor and Walker (1951) have found that an antidiuretic substance appears in the urine after smoking, and have shown that this substance is not nicotine. The substance resembles the hormone of the posterior lobe, inasmuch as it is destroyed by exposing it to the action of N/NaOH for one hour at room temperature. These observations have been confirmed by G. P. Burn and R. Singh Grewal (unpublished), who have shown that the intravenous injection of nicotine also gives rise to the appearance of the antidiuretic substance in the urine.

Thus the evidence that nicotine acts in man in the same way as acetylcholine acts in the dog is strong, and we can conclude that stimulation of the supraoptic nucleus is one of the effects of smoking.

The Vasopressor Hormone

That smoking should release the antidiuretic hormone of the posterior lobe appears at first sight to be of no more than theoretical interest, until it is remembered that this hormone is believed to be identical with the pressor hormone which causes vasoconstriction. In 1928 Kamm and his colleagues separated posterior-lobe extract into two fractions, oxytocin and vasopressin, of which the former possessed the action on the uterus, while the latter possessed the vasoconstrictor action and the antidiuretic action as well. We are therefore faced with the situation that smoking probably liberates in the blood a substance causing vasoconstriction, and must attempt to decide whether the amount liberated may cause constriction of the coronary vessels in the heart.

On this point we have no direct evidence from man to offer, and we are obliged to base our inferences on observations in the dog. We have been able to demonstrate that nicotine has a constrictor action on the coronary vessels of the dog (Bülbring, Burn and Walker, 1949). To do this it is necessary in the first place to arrange that in the anaesthetized animal in which the observations are made the general blood pressure should remain constant. The general blood pressure provides the driving force for the coronary flow, and, unless this pressure is stationary, changes in coronary flow cannot be attributed to changes in the calibre of the coronary vessels.

To ensure a constant blood pressure we attached the femoral artery of the dog to a reservoir of dog's blood (containing heparin). By connecting the reservoir to a 20-litre vessel containing air at a pressure of 130 mm. of mercury, changes of blood pressure in the dog were excluded. When the dog's blood pressure would otherwise have risen, blood was driven out into the reservoir; when the dog's blood pressure would have fallen, blood entered the dog from the reservoir. The dog was given artificial respiration and its chest was opened. A cannula was then inserted through the tip of the right auricle into the coronary sinus, to collect that fraction of the coronary venous blood which issues into the right auricle at that point. It is about 60% of the total coronary flow. This blood was conducted back through a tube to the dog's right external jugular vein, but the rate of flow could be measured at any moment from a T-piece in this tube.

In this preparation we then studied the effect of injecting nicotine into a vein at a uniform rate during a period of 10 minutes. Now it is known from other experiments that the direct effect of nicotine on the coronary vessels is to cause dilatation. In accordance with this we found that the first effect of the nicotine, given in a total of 1.3 mg. to a dog of 15 kg., was to cause dilatation, but that later the dilatation gave place to a progressive vasoconstriction which in 20 minutes reduced the initial coronary flow from, for example, 100 ml. to 93 ml. a minute. This dog was anaesthetized with pentobarbitone sodium, and it is likely that the anaesthetic diminished the effect of nicotine on structures such as the supraoptic nucleus. Thus we obtained evidence of two effects of nicotine on the coronary flow: the first a dilator action presumably due to a direct action on the coronary vessels, and the second a constrictor action supervening later, such as might be due to the release of the posterior-lobe hormone. We were in fact able to imitate this constrictor action by giving posterior-lobe extract intravenously at a rate of 3.3 milliunits a minute.

The Threshold Dose of Posterior-lobe Extract

We carried out a further series of experiments to determine what concentration of posterior-lobe extract was sufficient to cause some vasoconstriction of the coronary vessels in the absence of any anaesthetic. We wished to learn what was the threshold dose. We performed these experiments in the well-known Starling heart–lung preparation in which the central nervous system is excluded, and found that amounts ranging from 5 to 100 milliunits added to a circuit containing about 1 litre of blood produced a reduction in coronary flow in each of the 26 trials, the reduction varying from 2 to 25%.

In 11 trials the amount injected was 20 milliunits and the mean reduction in flow was 13%, this being the effect both when the injection was made into the superior vena cava and when it was first diluted in the reservoir of blood before it reached the heart. From these experiments we learnt that a concentration of 20 milliunits of pituitary (posterior lobe) extract per litre is above the threshold dose necessary to produce coronary constriction. The question then arose whether, in a man who has about 5 litres of blood, smoking would liberate a quantity of 100 milliunits, which would then give a similar concentration of the hormone.

Estimation of Hormone Released by Nicotine

A brief statement has been published by Lewis and Chalmers (1950) of experiments they have made which show that there is a linear relationship between the duration of the inhibition produced in man by graded intravenous doses of pitressin and the logarithmic dose. Having obtained the relation, they observed the duration

of inhibition caused by nicotine and then calculated the amount of hormone liberated by nicotine. They say that study of 21 normal subjects showed that the inhalation of cigarette smoke until severe malaise results releases an amount of antidiuretic hormone equivalent to more than 100 milliunits of pitressin.

Similar observations have been made at Oxford by G. P. Burn and R. Singh Grewal (unpublished). They also found that the period of antidiuretic action is proportional to the logarithm of the dose of posterior-lobe extract given intravenously.

A good many observations have already been made of the duration of the inhibition caused by smoking cigarettes. These are recorded in the Table, which

The Antidiuretic Effect of Cigarette-smoking

Author	Subject	No. of Cigarettes	Inhibition (min.)	Equiv. P.L.E. (milliunits)
Burn *et al.* (1945) ..	L.H.T.	3	210	>1,000
		3	120	190
	E.M.V.W.	3	210	>1,000
		1	105	90
	J.H.B.	1	195	>1,000
	T.H.C.L.	2	180	>1,000
	J.R.W.G.	2	195	>1,000
Walker (1949) ..	A (N)	1	165	>1,000
	B (N)	1	165	>1,000
	C (N)	1	120	190
	D (N)	1	105	90
	E (S)	1	75	18
	F (S)	1	60	7
	G (S)	1	60	7
	H (S)	2	180	>1,000
	J (S)	2	120	190
	K (N)	2	90	40
	L (S)	2	90	40
	M (S)	2	60	7
	N (S)	2	45	3
G. P. Burn and R. Singh Grewal	B	2	105	85
	B	2	105	85
	A	2	195	>1,000
	A	1	105	85

N = Non-smoker. S = Smoker.

shows that the inhibition caused by two cigarettes may be as short as 45 minutes, while at the other extreme the inhibition caused by one cigarette may be as long as 195 minutes. From the relation between dose and effect determined by Burn and Grewal the equivalent dose of posterior-lobe extract which would have produced the same inhibition was calculated, and this dose appears in the right-hand column of the Table. The range of doses of posterior-lobe extract injected to determine the curve did not exceed 1,500 milliunits, and, since it is dangerous to calculate from an extrapolated portion of the curve, the equivalent dose of posterior lobe extract is put down as "$>$ 1,000 milliunits," when the delay indicated the liberation of a greater amount than 1,000 milliunits.

It is important to say that in most experiments in which these large amounts of hormone were released in the blood there were signs of toxic effects such as pallor, sweating, nausea, and occasionally vomiting. If, then, we are to arrive at an estimate of what amount of hormone is released in ordinary smoking, these high figures should be excluded. They leave us with figures ranging from 3 up to 190 milliunits, the figure of 190 milliunits corresponding to the smoking of one, two, or three cigarettes according to the sensitiveness of the individual. The mean of these figures is 75 milliunits, though it is clear that different subjects vary so much that this mean figure has little individual application. Nevertheless, this mean figure indicates that, so far as the evidence goes, amounts of hormone may be liberated in ordinary smoking which are above the threshold for causing coronary constriction.

Practical Conclusions

At this point the scientific evidence ends, at least for the moment, and it remains to consider its practical application, if there is one. Those who train athletes for rowing or cross-country running have long maintained that smoking impairs performance. Probably the evidence now presented accounts for the trainer's view. As few of us, however, are engaged in athletics, the observations scarcely apply to us.

We know little or nothing about the fate of nicotine in the body, but it seems that as we grow older our power to destroy it diminishes. I draw this conclusion from the immunity which many young people seem to have to excessive smoking, and from the observation that many of my colleagues smoke less as they grow older and often stop altogether because they feel it affects their health. There is nothing improbable in the idea that the power to destroy nicotine, which represents tolerance of nicotine, declines with advancing years. If this is so, surely it is clear that those of advancing years who show signs of cardiac irregularity or of coronary involvement should be told not to smoke, because smoking involves some unknown degree of restriction of coronary circulation. We have recently seen evidence from Morris (1951) that during the last 50 years there has been a steady increase in death from coronary disease, which became marked after the 1914–18 war. Of course, that increase can be correlated with many other increases which have occurred in the same period, as, for example, with the increase in the use of motor-cars. However, it is true that in the same period there has been a great increase in the use of tobacco. In 1910 the amount imported which was retained for home consumption was 86,000,000 lb.; in 1942 it was 235,000,000 lb., or almost three times as much. It is possible that smoking is a contributory factor to coronary accidents.

Summary

Smoking, or the intravenous injection of nicotine, can be shown to inhibit a diuresis caused by drinking water in man.

The inhibition is due to the release of the antidiuretic hormone from the posterior lobe of the pituitary, because this hormone is found in the urine after smoking.

This hormone is believed to be the same as vasopressin, which constricts blood vessels, including the coronary vessels.

Nicotine produces a coronary constriction in the dog.

Ordinary smoking of one or two cigarettes liberates in man from 3 to 190 milliunits. Concentrations equal to 100 milliunits in 5 litres of blood are sufficient to cause coronary constriction in the coronary vessels of the dog, and may therefore have the same effect in man.

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