THE JOURNAL OF INVESTIGATIVE DERMATOLOGY
Vol. 49, No. 1

Printed in U.S.A.

GENERAL SWEATING ON THE HAIRY SKIN OF THE DOG AND ITS MECHANISMS*

TAKAYUKI IWABUCHI, M.D.

Beginning with the early work of Gurlt (1), it has been shown that the hairy skin of the dog possesses sweat glands (2–7), which are of apocrine type (4–6). Recently Aoki and Wada (8) and Aoki (6) demonstrated that the sweat glands are responsive to intradermal injections of sympathomimetic drugs, such as adrenaline and noradrenaline, and also to those of parasympathomimetic drugs, such as acetylcholine, mecholyl and pilocarpine. Nevertheless, little is known about the mechanism by which the secretory function of the sweat glands in the canine hairy skin is normally controlled.

This presentation deals with the evidence that catecholamines of the adrenal medulla are capable of provoking general sweating on the hairy skin of the dog, and also with the evidence that these sweat glands receive adrenergic innervation from the sympathetic nerve.

MATERIALS AND METHODS

Observations were made on 17 mongrel dogs of both sexes about 7 months to 5 years of age and 5.5 to 18.5 kg in weight. Each animal was fastened to an animal board in the supine position mostly without anesthesia, and the ventral surface of the thorax and abdomen were used as test areas for sweating. The hairs of these areas were clipped with electric clippers. To visualize sweat as black dots or spots at the openings of active sweat gland ducts, the iodine-starch method of Wada and Takagaki (9, 10) was used. The skin was painted with 3% iodine in absolute alcohol and dried; then it was covered with a mixture of corn starch and castor oil (about 1:1 in volume).

In the first series of experiments, the effects of infusion of adrenaline and noradrenaline on sweating were studied in 12 dogs. Four kinds of infusion rates of adrenaline or noradrenaline, 1, 3, 6 and 10 μg/kg.min, were used. Just before the experiment, solutions of adrenaline or noradrenaline for infusion were prepared so that a total amount of each agent to be infused for 30 minutes was contained in 50 ml of 0.9% NaCl solution. Each test solution was continuously injected at a rate of 5/3 ml per minute into the saphenous vein, using a motor-driven syringe for a period of 21 minutes, unless otherwise noted. For this purpose the saphenous vein was exposed under local anesthesia with 2% procaine hydrochloride solution; and tied into it was a polyethylene cannula which was connected to the syringe with a thin polyethylene tube. On infusion, care was taken to keep the dead space for infusion as small as possible. In each experiment one or two kinds of infusion rates of each agent were tested. When two infusions were successively made, the first infusion was made at the rate of 1 or 3 μg/kg.min, and at about 5 to 15 minutes after the end of the first infusion the second infusion was started at the rate of 6 or 10 μg/kg.min. When sweating was evoked by the first infusion, the skin was wiped with cotton pledgets moistened with absolute alcohol and the indicator materials were applied again, in order to make sure that sweating had ceased before the start of the second infusion.

Prior to the infusion of a test solution of adrenaline or noradrenaline, and about 10 minutes after the animal was fastened to the animal board, a control infusion of 0.9% NaCl solution was performed for 6 minutes.

In the second series of experiments, the effect of asphyxiation on sweating was examined on 12 dogs, including 7 dogs which were used for the first series of experiments. For this purpose, the mouth and nose of the animal, mostly under non-anesthesia, were wrapped with a wet towel for 2 to 9 minutes until the respiratory movements almost ceased.

In 3 of the 12 dogs, thoracic sympathectomy was performed according to the technic described by Wada (11). The animal was anesthetized by intravenous injection of pentobarbital sodium (30 mg/kg) and maintained on artificial respiration. A transverse incision about 15 cm in length was made on the skin of the lateral side of the middle thorax. The 4th and 8th ribs about 8 cm in length were resected and the chest was opened. The sympathetic chain on the left side was removed from the level of the stellate ganglion to that of the 10th rib in 3 dogs, except one dog in which a portion of the chain from the level of the 7th rib to that of the 8th rib was left behind.

In both series of experiments, the secretion of catecholamines from the adrenal glands was minimized in some dogs either by section of the major and minor splanchnic nerves on one side combined with adrenal medullectomy on the other side, or by bilateral adrenal medullectomy. These operations were carried out aseptically at two sittings with the interval of 6 to 8 days through the lumbar or abdominal route under anesthesia with pentobarbital sodium. Afterwards, the adrenal gland on the splanchnicotomized side was medullectomized for the reason that a complete denerva-

Received for publication October 17, 1966.
* From the Physiological Laboratory and the First Department of Internal Medicine, Tohoku University School of Medicine, Sendai, Japan.

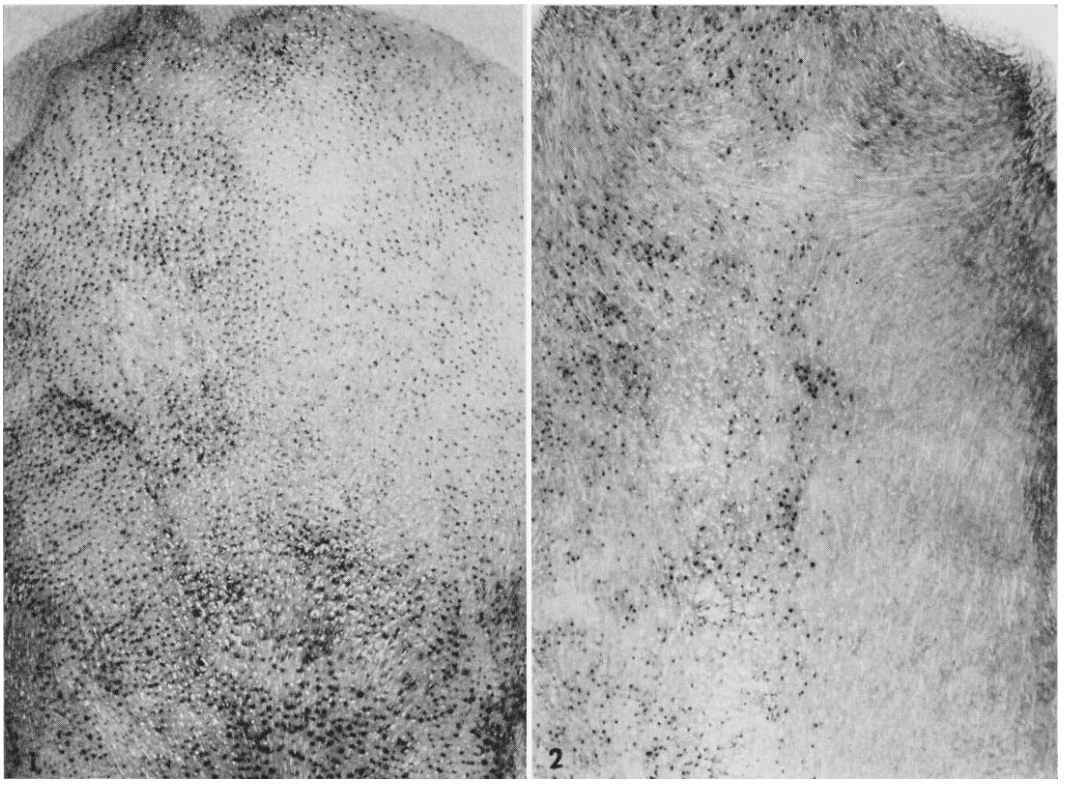

FIG. 1. Sweat response on the ventral surface of the thorax to intravenous infusion of adrenaline at 6 μg/kg.min. Photographed 18 minutes after the start of infusion. Sweating is visualized as black spots by the method of Wada and Takagaki. Reduced to ¾.

FIG. 2. Sweating provoked by asphyxiation on the ventral surface of the thorax of the dog in which left thoracic sympathectomy and bilateral adrenal medullectomy had been performed. Sweating is absent on the denervated side (to the right), and non-sweating areas are demarcated by the midline. × 1.2.

tion of the glands could not be achieved by the section of the above-mentioned nerves. The adrenal medullectomy was performed either through the lumbar or abdominal route. After the adrenal vein and small arteries supplying the gland had been ligated close to the gland, it was opened by a T-shaped incision and the medullary tissue was removed as completely as possible with a small spoon and a brush.*

The degree of sweat response was roughly designated as slight, moderate, and strong. In a slight response some tens to some hundreds of sweat spots were scattered sparsely over the frontal surface of the thorax and abdomen. In a moderate response innumerable sweat spots appeared, but unevenly. A strong response was such that sweat spots were almost evenly and densely distributed, indicating that the great majority of the sweat glands were active, as illustrated in Figure 1.

* The surgical procedures were performed in cooperation with Prof. Masao Wada.

The sensitivity of the sweat glands to adrenaline or noradrenaline injected intradermally in 0.2 ml was estimated by determining the minimum effective concentration of each agent for producing sweat spots evenly over the wheal of injection. For this purpose, the lateral part of the frontal surface of the thorax was used as a test area.

The drugs used during these experiments were l-adrenaline hydrochloride (Sankyo), dl-noradrenaline (Sankyo), l-noradrenaline bitartrate (Winthrop), Mecholyl chloride (Merck), dihydroergotamine methanesulphonate (Sandoz) and atropine sulfate (J. P.). Concentrations of adrenaline and noradrenaline were given in terms of the ions, and those of the other agents in terms of the salts. When these agents were injected intradermally, the solutions of these agents were prepared in 0.9% NaCl solution at graded concentrations just before use, and 0.2 ml of the solutions was injected with a tuberculin syringe. As a control, the same amount of 0.9% NaCl solution was used.

The experiments were performed at room tem-

perature of 6.5 to 29° C. and at relative humidity of 53 to 92%.

RESULTS

Most of the dogs struggled more or less violently when they were fastened to the animal board. Under such conditions, however, no definite sweating was found on the ventral surface of the thorax and abdomen in most of the dogs. In a few dogs, a slight but definite sweating was often observed. In one instance a moderate sweating occurred in association with a vigorous struggling: sweating appeared at first in a part of the abdominal surface, but in a few minutes it extended over the whole surface of the abdomen and thorax, although the density of sweat spots was lower in the thorax than in the abdomen.

It should be noted that the sweat spots which appeared in the skin areas of hyperemia due to dermatitis, or in the areas closely adjacent to the wounds produced by hair clipping and any other causes, were discarded because the mechanism was obscure.

The Sweat Response to Continuous Intravenous Injections of Adrenaline and Noradrenaline

The results obtained in this series of experiments are noted in Table I. During infusions of adrenaline and noradrenaline, as well as of 0.9% NaCl solution as a control, most of the test animals showed no noticeable signs of emotional excitement. Therefore, it seems proper to assume that the sweat responses to be described below might be mainly due to the sudorific properties of adrenaline and noradrenaline. Usually, a preceding infusion of 0.9% NaCl solution elicited no definite sweat response.

Infusion of adrenaline.—Continuous intravenous injections of adrenaline were made at the rate of 1, 3, 6 and 10 μg/kg.min in 9 dogs, and at the rate of 10 μg/kg.min only in 3 other animals.

At the rate of 1 μg/kg.min, the adrenaline infusion elicited a slight response in one-third of 9 tests on 9 dogs and no response in the other tests. Similar results were obtained at the rate of 3 μg/kg.min, but a moderate sweating was observed in one dog. When the rate of adrenaline infusion was increased up to 6 μg/kg.min, the sweat response occurred in all 9 tests on 9 dogs: it was strong in 3 tests, moderate in 1 and slight in the remaining 5. An example of strong sweating response to adrenaline is illustrated in Figure 1. Likewise, at the rate of 10 μg/kg.min, all of 16 tests on 12 dogs showed sweating: the response was strong in 7 tests, moderate in 5 and slight in 4.

The latent period between the start of adrenaline infusion and the appearance of sweat spots showed a considerable variation in different tests, ranging from 55 seconds to 7 minutes. When the dead space for infusion was

TABLE I

Sweat responses to continuous infusions of l-adrenaline (Adr.) and l-noradrenaline (Nadr.)

Rate of infusion	Agent	Degree of sweat response			
		No response	Slight	Moderate	Strong
1 μg/kg.min	Adr.	6 + 3*	3 + 1* + 1†	0	0
	Nadr.	2	1	0	0
3 μg/kg.min	Adr.	3	5 + 2*	1 + 1* + 1†	0
	Nadr.	2	1	0	0
6 μg/kg.min	Adr.	0	5 + 1*	1	3 + 2* + 1†
	Nadr.	0	2	0	1
10 μg/kg.min	Adr.	0	4	5	7 + 3*
	Nadr.	0	1	1	1

Numerals in columns of degree of sweat response indicate the number of tests.

* Tests in dogs whose splanchnic nerves were sectioned on the left side and the adrenal gland medullectomized on the right side.

† Tests in a dog whose adrenal glands were medullectomized.

taken into consideration, the obtained values were not very exact, but it was found that the latent period was shortened as the rate of adrenaline was increased: at 1 μg/kg.min, it was 5 minutes and 40 seconds on the average; at 3 μg/kg.min, 2 minutes and 55 seconds; at 6 μg/kg.min, 2 minutes and 8 seconds; and at 10 μg/kg.min, 1 minute and 24 seconds.

When a slight or moderate sweat response was elicited by the infusion of adrenaline at 1 or 3 μg/kg.min, sweat spots were first observed in some parts of the ventral surface of the thorax and abdomen, and slowly increased in number, until the infusion was stopped at 21 minutes after the start of infusion. When a strong response was produced by adrenaline at 6 and 10 μg/kg.min, sweat spots rapidly increased in number and almost reached their highest density at between 9 and 18 minutes and between 3 and 18 minutes after the start of the infusion, respectively.

The degree of sweat response to each rate of adrenaline infused seemed to depend at least partly upon the sensitivity of the sweat glands themselves to intradermal adrenaline. The minimum effective concentrations of adrenaline injected intradermally for eliciting sweat response on the injection wheal ranged from 10^{-7} to 10^{-4} in the dogs used in the above experiments, although the sensitivity to adrenaline was not always steady even in one and same animals. In dogs which showed sweat response to adrenaline at 1 and 3 μg/kg.min, the threshold effective concentration of adrenaline was 10^{-7}. Further, with adrenaline at 6 and 10 μg/kg.min, a strong response was observed only in the dogs with the threshold effective concentrations of 10^{-7} and 10^{-6}.

The duration of strong sweat response to adrenaline at 6 and 10 μg/kg.min was studied in 4 dogs, and it was found that the sweating had ceased within 4 to 10 minutes after the end of infusion.

Similar experiments were performed in 4 dogs with adrenomedullary secretion minimized. In 3 dogs, adrenal medullectomy of the right adrenal gland and splanchnicotomy of the left side were carried out separately with an interval of about 1 week. At 1 to 10 weeks after the last operation, adrenaline was infused at the rate of 1, 3, 6 and 10 μg/kg.min. As shown in Table I, all of the 3 dogs showed definite sweat responses to adrenaline infused at the rate of 3, 6 and 10 μg/kg.min, whereas 3 out of 4 tests on 3 dogs with adrenaline at 1 μg/kg.min showed no response. Further, in another dog with the adrenal glands demedullated at two sittings adrenaline was infused at the rate of 1, 3 and 6 μg/kg.min about 3 weeks after the last operation; a more or less remarkable sweating was provoked by all of these rates, as shown in Table I. There was found no material difference between the normal and operated animals in the degree and pattern of sweat response to each rate of adrenaline infusion. The minimum effective concentration of adrenaline intradermally injected was 10^{-7} in all.

To determine whether strong sweat responses to adrenaline at 6 and 10 μg/kg.min are influenced by successive infusions of the same rates of adrenaline, three experiments were performed on two normal dogs. In one dog the second infusion of adrenaline at 6 μg/kg.min was started about 10 minutes after the end of the first one which lasted for 20 minutes, and was continued for 12 minutes. Likewise, in another dog about 10 minutes after the first infusion of adrenaline at 10 μg/kg.min for 10 or 12 minutes, the second one was started and continued for 10 minutes. There was, however, no significant difference in the degree of response between the two successive infusions. In one experiment on successive tests with adrenaline at 10 μg/kg.min, sweat spots in the same skin area were photographed at the end of each infusion according to the technic described by Mellinkoff and Sonnenschein (12). It was found that about 80 per cent of the sweat glands responded to both infusions. Thus, in these experiments there was not definite evidence of refractoriness of the sweat glands to the repeated infusion of adrenaline.

On the other hand, it was shown in some experiments that at the site of the wheal produced by intradermal injection of adrenaline in an effective concentration of 10^{-7} or 10^{-6} the sweat glands did no longer respond to a subsequent infusion of adrenaline at 6 or 10 μg/kg.min lasting for 13 to 21 minutes. This refractoriness was found to continue for at least 1 hour after the intradermal injection. The same was true of intradermal mecholyl in 10^{-6} and 10^{-5}. It may be noted that such refrac-

toriness was not observed at the control injection wheal with 0.9% NaCl solution.

Infusion of noradrenaline.—Additionally, sudorific effect of infusion of noradrenaline at 1, 3, 6 and 10 μg/kg.min was studied in 5 normal dogs: l-noradrenaline was infused in 2 dogs, dl-noradrenaline in another 2 dogs and both agents in the remaining one.

As indicated in Table I, the sudorific effect of l-noradrenaline at 1 and 3 μg/kg.min was inconstant, while at 6 and 10 μg/kg.min it elicited a more or less vigorous sweat response in all 6 tests. Thus the results obtained with l-noradrenaline were similar to the above-described results with l-adrenaline.

The minimum effective concentrations of l-adrenaline and l-noradrenaline were determined at the same time in 9 experiments on the 5 dogs. In most of the experiments the threshold effective concentrations were identical for both agents and ranged from 10^{-8} to 10^{-6}.

Further, the effect of dl-noradrenaline was examined in 12 tests on 3 dogs. The results obtained are not presented in Table I, for the sake of simplicity. At 1 and 3 μg/kg.min, the infusion of dl-noradrenaline resulted in a slight sweating in 3 of 6 tests on 3 dogs, while at 6 μg/kg.min sweating was slight in one test and strong in 2 tests. At 10 μg/kg.min, the response was strong in all 3 tests. In one animal to which both kinds of noradrenaline were infused at four different rates, the infusions of l-noradrenaline were always effective, but dl-noradrenaline effected no definite sweating at the rate of 1 and 3 μg/kg.min, in spite of the fact that the threshold effective concentrations of intradermal l- and dl-noradrenaline were determined always as 10^{-7} on the days of infusion experiment with each agent. In another dog the threshold effective concentration determined at the same time was 10^{-6} for both dl- and l-noradrenaline.

Effects of dihydroergotamine and atropine intradermally applied on the sweating caused by infusion of adrenaline or noradrenaline.—Dihydroergotamine (DHE) and atropine at graded concentrations were intradermally injected 6 to 18 minutes prior to the infusion of adrenaline or noradrenaline at the rate of 6 and 10 μg/kg.min, which was sufficient to elicit a strong sweat response. Blocking effects of the drugs were determined at 5 to 15 minutes after the start of the infusion. Control intradermal injection was made with 0.9% NaCl solution. Effects of DHE and atropine on the sweating induced by adrenaline infusion were studied in 5 experiments on 2 dogs. At concentrations of 10^{-5} to 10^{-6}, DHE inhibited completely the sweating at the site of injection wheal in all 10 tests, in contrast to the usual sweat response on the control wheals. With DHE in 10^{-7}, an almost complete inhibition was obtained in 4 tests, and incomplete inhibition in 1 test. In contrast, atropine in 10^{-7} to 10^{-6} showed no inhibition in all 10 tests. With atropine in 10^{-5}, however, an incomplete inhibition was observed in 4 out of 5 tests, and no inhibition in the remaining one.

Similarly, in 3 experiments on 2 dogs, effects of the both drugs on the strong sweat responses to noradrenaline infused were examined. The sweating was completely inhibited by DHE in 10^{-5} to 10^{-6} in all 6 tests, and even with DHE in 10^{-7} the inhibition was almost complete in 1 of 3 tests and incomplete in the other 2. With atropine in 10^{-5}, an incomplete inhibition was observed in 1, and no inhibition was obtained in 2 tests. At 10^{-6} to 10^{-7}, atropine did not affect the sweating produced by noradrenaline infusion in all 6 tests.

Thus, the results indicate that the sweating produced by infusion of adrenaline and noradrenaline is blocked easily by DHE, but is very resistant to blocking action of atropine.

Sweating Caused by Asphyxiation

The observation described above has raised the question whether or not general sweating is caused by catecholamines discharged from the adrenal glands. Then the effect of asphyxia which has been known to increase the adrenomedually secretion was examined. For this purpose the nose and mouth of dogs were wrapped with a wet towel for about 2 to 9 minutes under non-anesthesia. In the beginning of asphyxiation the animals struggled more or less violently.

A more or less vigorous sweating was caused by asphyxiation in 12 out of 14 experiments on 10 normal dogs: the response was slight in 4 experiments, moderate in 3 and strong in 5. Sweat spots became visible at about 30 seconds

to 4 minutes after the start of asphyxiation. The sweat response to asphyxiation was also observed in 3 dogs in which catecholamine secretion had been minimized by medullectomy of the right adrenal gland and splanchnicotomy on the left side, and likewise after a subsequent medullectomy of the adrenal gland of the splanchnicotomized side had been performed. The same finding was obtained in another dog with both adrenals medullectomized. It should be noted that a definite sweating could be evoked by asphyxiation in 2 dogs anesthetized with pentobarbital sodium. There was no relationship between the degree of the sweat response and the sensitivity of the sweat glands to adrenaline intradermally administered.

Effects of DHE and atropine on the sweating evoked by asphyxiation.—The experiments were carried out in 3 normal dogs and in 4 dogs of which adrenomedullary secretion had been interfered with by adrenal medullectomy on one side and splanchnicotomy on the other side, or by adrenal medullectomy on both sides.

DHE and atropine in graded concentrations were intradermally injected 6 to 18 minutes before asphyxiation was begun. The results obtained are summarized in Table II

DHE in 10^{-8} scarcely affected the sweat response to asphyxia on the injection wheals. With DHE in 10^{-7}, the inhibition was almost complete in most of the tests. DHE in 10^{-6} to 10^{-5} was effective in abolishing completely the sweating produced by asphyxiation.

In contrast, atropine was less effective in blocking the sweat response to asphyxiation. With atropine in 10^{-7}, the great majority of the tests showed no inhibition. With atropine in 10^{-6}, the inhibition was incomplete in about a half of the tests, and the remaining tests showed complete or no inhibition. At the concentration of 10^{-5}, atropine showed a complete inhibition in most of the tests and an incomplete or no inhibition in a small number of tests. The variations in the effectiveness of atropine in identical concentrations might be at least partly due to the difference in intensity of sweating produced by asphyxiation. At any rate, it is significant that the sweat response to asphyxiation was easily affected by DHE, but not by atropine.

Effect of thoracic sympathectomy on the sweating evoked by asphyxiation.—It was of interest to note that the sweating by asphyxiation was never abolished by demedullation of the adrenal glands. This suggested that a nervous mechanism might be involved in this

TABLE II

Effects of intradermal injections of DHE and atropine on sweating produced by asphyxiation

Concentration	Degree of inhibition	DHE			Atropine		
		Adrenomedullary secretion		Total	Adrenomedullary secretion		Total
		Normal	Impaired		Normal	Impaired	
10^{-8}	Complete	0	0	0			
	Incomplete	1	0	1			
	No	0	4	4			
10^{-7}	Complete	4	5	9	0	1	1
	Incomplete	0	2	2	1	1	2
	No	0	0	0	3	5	8
10^{-6}	Complete	4	7	11	1	2	3
	Incomplete	0	0	0	2	4	6
	No	0	0	0	1	1	2
10^{-5}	Complete	3	4	7	2	4	6
	Incomplete	0	0	0	0	1	1
	No	0	0	0	1	0	1

Numerals in columns of DHE and atropine indicate the number of tests.

The tests were performed in 3 normal dogs and in 4 dogs whose adrenomedullary secretion had been impaired.

sweating. Then, the effect of removal of the thoracic sympathetic chain on the sweating by asphyxiation was studied in 3 dogs. In 2 of them the sympathetic chain from the level of the stellate ganglion to the level of the 10th rib was removed. The experiments on asphyxiation were performed repeatedly for a period between 5 and 36 days after the nerve operation. It was found that usually the sweat response elicited by asphyxiation in these two dogs was markedly diminished or almost completely abolished in the skin areas extending downwards to almost the level of the umbilicus on the operated side. It is noteworthy that when sweating was produced on the operated side by asphyxiation, the response appeared, though to a minor degree, about 1 to 2 minutes after the asphyxiation was discontinued, while on the normal side the usual sweat response began to appear during the course of asphyxiation. In these dogs the experiments on asphyxiation were repeated at 5 to 51 days after the adrenal demedullation on both sides. The delayed sweating on the sympathectomized side could no longer be observed. In another dog the thoracic sympathectomy was performed in the same way, but a portion of the chain from the level of the 7th rib to the level of 8th rib was left behind. In this dog, the sweating on asphyxia was almost completely abolished on the operated side, particularly after the bilateral adrenal demedullation except the sweating which appeared restricted to the band-shaped areas in the lower one-third of the thorax, corresponding roughly to the dermatomes innervated by Th7 and Th8. The areas which were devoid of sweat spots in these three dogs were almost sharply demarcated by the midline, as illustrated in Figure 2. It was proved that such a phenomenon could not be seen when a dummy operation such as incision of the skin together with underlying tissues was performed. It must be noted that in these 3 dogs the adrenaline infusion at the rate of 6 or 10 μg/kg.min elicited sweating not only on the normal side, but also on the sympathectomized side; there was no significant difference in the degree of sweating between the two sides in all these dogs.

The effect of sympathectomy on the sensitivity of the sweat glands was studied in these 3 dogs by determining the effective concentrations of intradermal adrenaline. The sensitivity of the sweat glands in the skin of the sympathectomized side was found to remain identical with that on the normal side.

Sweating Evoked by Stretching the Skin

The hairy skin of the dog showed a definite sweating when the skin, about 5 to 10 cm in length, was stretched for a few seconds with the finger tips in opposite directions and with an appropriate force. However, unidirectional stretching of the skin was less effective. Sweat spots became visible within 10 to 60 seconds after stretching the skin, and were distributed linearly in the area stretched. Such sweating could be produced everywhere on the ventral aspect of the thorax or abdomen, but lasted only for a few minutes, although the intensity of sweating was often not the same in different skin areas even in the same dogs. It was occasionally noticed that the sweating was provoked on the same areas more than twice by repetition of stretching, but in the second stretching test the majority of the sweat spots were found at the pores of sweat glands which did not show sweating to the first stretching test. It is noteworthy that the sweating on stretching the skin could be seen also in the areas deprived of sympathetic innervation in the dogs with the adrenal glands medullectomized.

DHE and atropine injected intradermally at concentrations ranging from 10^{-7} to 10^{-5} did not affect this sweating.

DISCUSSION

Evans and his co-workers (13–16) put forward an attractive conception that general sweating in the horse is controlled normally by adrenaline secretion from the adrenal medulla. However, there is as yet no satisfactory experimental evidence that the adrenomedullary secretion participates in the production of sweating in man and animals.

The primary aim of the present investigation was to determine whether the apocrine sweat glands of the hairy skin of the dog are stimulated by catecholamines from the adrenal glands.

Satake and his colleagues studied precisely the rate of adrenomedullary secretion in non-anesthetized dogs under various experimental

conditions, and their experimental results were codified by Satake (17). In their experiments, however, catecholamines from the adrenals were estimated as adrenaline. In resting condition the secretion rate was of the order of 0.05 μg/kg.min, but it increased more or less considerably according to the effectiveness of the stimuli. The higher extreme in the range of the rate was found to be of the order of 20 μg/kg.min (18). These values can be regarded as approximate to those of the catecholamines, because the bio-assay method used in their experiments has almost the same sensitivity to adrenaline and to noradrenaline, and because the largest part of the catecholamines is adrenaline, according to Houssay and Rapele (19) and Malméjac (20, 21).

Accordingly, in the present experiments intravenous infusions of adrenaline and additionally of noradrenaline were performed at rates of 1, 3, 6 and 10 μg/kg.min for each agent, and it was found that general sweating could be produced by both catehcolamines at the rate of 6 and 10 μg/kg.min in all of the dogs tested, and at the rate of 1 and 3 μg/kg.min in some dogs. The degree of the sweating produced by each rate of infusion seemed to depend at least partly upon the sensitivity of the sweat glands to both the catecholamines. There was no significant difference in the sudorific potencies between adrenaline and noradrenaline, whether they were applied systemically or intradermally. Thus, the results suggested the possibility that general sweating can be induced by circulating catecholamines, when their secretion is increased up to the rate of 1 μg/kg.min or more.

Aoki (6) showed that in the hairy skin of dogs the sweat glands which had been once stimulated by intradermal injection of adrenaline showed a long-lasting refractoriness. This was confirmed by the present experiments. But there was no definite evidence of the refractoriness when the effects of two successive infusions of adrenaline were compared.

Then, an attempt was made to determine whether or not asphyxiation of the animal, which has been known to be a potent stimulus for the adrenomedullary secretion, is capable of inducing sweat response in non-anesthetized dogs. According to Sato *et al.* (22), the rate of the secretion of catecholamines estimated as adrenaline, was increased by asphyxia to 3.1 μg/kg.min at maximum and to 0.8 μg/kg.min on the average in non-anesthetized dogs. Therefore, the effect of asphyxiation was tested by using the same procedure as described by these investigators; it was found that a more or less vigorous sweating occurred on asphyxiation in most of the dogs tested. This sweat response would at first seem to be due to the catecholamines from the adrenals. But, it was found that the sweating by asphyxiation could not be abolished by medullectomy of the adrenals. For analyzing the mechanism underlying the sweating, unilateral thoracic sympathectomy was performed. After this operation, the response to asphyxiation developed in the usual manner in the skin area of non-operated side, while it appeared delayed and to a minor degree in the area of the operated side. However, the latter response appeared no longer after medullectomy of the adrenals. From these results, it seems reasonable to conclude that the sweating on asphyxia was produced primarily through a nervous mechanism and subsidiarily through a humoral mechanism, that is, by the catecholamines released from the adrenals.

It is noteworthy that the sweat glands in the sympathectomized area responded to the adrenaline infusion almost to the same degree as those in normally innervated area. And, the sensitivity of the glands to adrenaline intradermally injected was found to remain unaltered after sympathetic denervation. This is in agreement with the observation of Aoki (6).

The present results indicate that the sweat response elicited by asphyxiation in dogs with the adrenals demedullated, was easily inhibited at the site of intradermal injection of DHE in relatively low concentrations. Atropine in relatively high concentrations was also effective in inhibiting the sweating. Similar results were obtained with DHE and atropine in the experiments on adrenaline infusion. Therefore, the inhibitory effect of atropine on the sweating produced by asphyxiation does not imply the presence of cholinergic component in the nervous mechanism. It seems rather reasonable to presume that the sweat glands of the dog's hairy skin are innervated by adrenergic sympathetic nerve fibers.

Further, it was confirmed by the present experiments that an axon reflex sweating cannot be produced by intradermal injection of nicotine in 10^{-5} to 10^{-3} (6, 8). This may be explained by assuming that the nerve fibers to the apocrine sweat glands in the hairy skin of the dog are devoid of receptors responsible for the sweating axon reflex. In contrast, it was demonstrated by Takahashi (23) that the sweat glands in the dog's footpads, eccrine in type, are supplied with sympathetic cholinergic nerve fibers possessing the axon reflex receptors.

From the present investigation, it is evident that the apocrine glands in the hairy skin of the dog is innervated by the sympathetic nerve. But there is as yet no confirmatory histologic evidence of their innervation. Hellmann (24) reported that there is no cholinesterase around the sweat glands in the hairy skin of the dog. This was confirmed by Aoki (personal communication).

Aoki (6) found that in certain dogs a slight sweating occurred in restricted areas such as around the umbilicus and in the hypogastric or pubic region, which became evident particularly after violent struggling and panting. Lemaire *et al.* (7) observed by the iodine-starch paper method that when the body temperature of dogs was elevated by application of radiant heat or by inhalation of hot air, general sweating appeared on the hairy skin, assuming that this sweating might be provoked through the central nervous mechanism. These sweat responses might be effected very probably through a nervous mechanism, but the possibility of humoral mechanism cannot be excluded.

It may be added that in the hairy skin of dogs a local transient sweating was induced by stretching the skin. This sweating could be obtained even in the denervated skin areas in dogs deprived of their adrenomedullary secretion, and could be inhibited neither by DHE nor by atropine, locally administered. In this respect, the response to stretching the skin differs in its underlying mechanism from that to asphyxiation.

Hurley and Shelley (25) described apocrine sweating in man after repeatedly stroking the axillary skin with a tongue blade and explained it to be a result of contraction of the myoepithelium of the glands. The sweating evoked by stretching the dog's hairy skin may be explained by assuming such mechanism, but further investigation is required before the mechanism can be clarified.

Finally, from the present results it seems reasonable to speculate on the possibility that the eccrine sweat glands in the general skin of the human subject can be stimulated by circulating catecholamines when its secretion from the adrenals is increased, since their sensitivities to adrenaline, evaluated as minimum effective concentrations, are comparable to those of the apocrine glands of the hairy skin of the dog (9, 10).

SUMMARY

Infusions of adrenaline and noradrenaline were made in non-anesthetized dogs at the rate of 1, 3, 6 and 10 μg/kg.min. At 6 and 10 μg/kg.min the infusions of adrenaline and noradrenaline caused general sweating on the hairy skin in all dogs tested, and even at 1 and 3 μg/kg.min, a definite sweating could be obtained occasionally. This finding suggests the possibility that general sweating can be produced on the hairy skin of the dog by circulating catecholamines when their secretion from the adrenals is increased.

Asphyxiation caused general sweating on the hairy skin of the dog. This sweating could not be abolished by bilateral medullectomy of the adrenal glands. The sweating on asphyxiation, however, did not occur on the sympathetically denervated skin, especially after deprivation of the catecholamine secretion from the adrenals. This fact points to the existence of a sympathetic innervation, very probably adrenergic in nature, to the apocrine glands in the dog's hairy skin. It seems reasonable to conclude that the sweating on asphyxiation is produced primarily through a nervous mechanism, and subsidiarily through a humoral mechanism.

REFERENCES

1. Gurlt: Vergleichende Untersuchungen über die Haut des Menschen und der Haus-Säugethiere, besonders in Beziehung auf die Absonderungsorgane des Haut-Talges und des Schweisses. Arch. Anat. Physiol., 399, 1835.
2. Claushen, A.: Mikroskopishe Untersuchungen über die Epidermalgebilde am Rumpfe des Hundes mit besonderer Berücksichtigung der Schweissdrüsen. Anat. Anz., *77*: 81, 1933–34.

3. Speed, J. G.: Sweat-glands of the dog. Vet. J., *97:* 252, 1941.
4. Nielsen, S. W.: Glands of the canine skin—morphology and distribution. Amer. J. Vet. Res., *14:* 448, 1953.
5. Roy, W. E.: Role of the sweat glands in eczema of dogs. J. Amer. Vet. Med. Ass., *124:* 51, 1954.
6. Aoki, T.: Stimulation of the sweat glands in the hairy skin of the dog by adrenaline, noradrenaline, acetylcholine, mecholyl and pilocarpine. J. Invest. Derm., *24:* 545, 1955.
7. Lemaire, R., Boura, M. and Quenum, A.: L'activité sécrétoire des glandes sudoripares chez le chien. J. Physiol. (Paris), *50:* 374, 1958.
8. Aoki, T. and Wada, M.: Functional activity of the sweat glands in the hairy skin of the dog. Science, *114:* 123, 1951.
9. Wada, M. and Takagaki, T.: A simple and accurate method for detecting the secretion of sweat. Tohoku J. Exp. Med., *49:* 284, 1948.
10. Wada, M.: Sudorific action of adrenalin on the human sweat glands and determination of their excitability. Science, *111:* 376, 1950.
11. Wada, M.: Der Einfluss der Kälteapplikation auf die Pulsfrequenz von Hunden mit ausgeschalteten extrakardialen Herznerven. Tohoku J. Exp. Med., *26:* 546, 1935.
12. Mellinkoff, S. M. and Sonnenschein, R. R.: Identity of sweat glands stimulated by heat, epinephrine, and acetylcholine. Science, *120:* 997, 1954.
13. Evans, C. L., Smith, D. F. G. and Weil-Malherbe, H.: The adrenaline and noradrenaline of venous blood of the horse before and after exercise. J. Physiol. (London), *128:* 50P, 1955.
14. Evans, C. L. and Smith, D. F. G.: Sweating responses in the horse. Proc. Roy. Soc., *145:* 61, 1956.
15. Evans, C. L., Smith, D. F. G. and Weil-Malherbe, H.: The relation between sweating and the catechol content of the blood in the horse. J. Physiol. (London), *132:* 542, 1956.
16. Bell, F. R. and Evans, C. L.: The relation between sweating and the innervation of sweat glands in the horse. J. Physiol. (London), *134:* 421, 1956.
17. Satake, Y.: Secretion of Adrenaline and Sympathins. Tokyo, Nanzando Co. Ltd., 1955.
18. Wada, M., Hirano, T. and Tiba, M.: A further study of the augmenting action of nicotine upon the epinephrine secretion from the suprarenals of the non-anaesthetized dog. Tohoku J. Exp. Med., *33:* 189, 1938.
19. Houssay, B. A. and Rapela, C. E.: Adrenal secretion of adrenalin and noradrenalin. Naunyn-Schmiedeberg Arch. Exp. Path., *219:* 156, 1953.
20. Malméjac, J.: Sur la nature de la sécrétion médullo-surrénale. Discussion des théories dualiste ou uniciste. Bull. Acad. Roy. Med. Belg., *23:* 50, 1958.
21. Malméjac, J.: Activity of the adrenal medulla and its regulation. Physiol. Rev., *44:* 186, 1964.
22. Sato, H., Inaba, T. and Takahashi, W.: The intensity of the augmented epinephrine liberation elicitable by asphyxiating the non-anaesthetized dog. Tohoku J. Exp. Med., *19:* 421, 1932.
23. Takahashi, Y.: Functional activity of the eccrine sweat glands in the toe-pads of the dog. Tohoku J. Exp. Med., *83:* 205, 1964.
24. Hellmann, K.: Cholinesterase and amine oxidase in the skin: a histochemical investigation. J. Physiol. (London), *129:* 454, 1955.
25. Hurley, H. J. and Shelley, W. B.: The Human Apocrine Sweat Gland in Health and Disease. Springfield, Illinois, Charles C Thomas, 1960.