EFFECTS OF ACTH, EPINEPHRINE AND ATROPINE ON THE BLOOD PICTURE OF THE DOG

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It was indicated by HARLOW and SELYE¹³⁾(1937) and SELYE³⁰⁾(1949) that very characteristic changes in the blood picture were obvious during the alarm reaction of the general adaptation syndrome. There was a pronounced increase in the total white blood count, due to neutrophilic leukocytosis with eosinopenia and relative, or even absolute, lymphopenia. THORN⁴¹⁾(1948) observed the remarkable eosinopenia in the circulating blood in case of the administration of adrenocorticotrophine (ACTH) and proposed the Thorn test, an activity test of the adrenal cortex by means of ACTH administration, based on the decrease of eosinophils, consequent on the release of glucocorticoids.

Although there were numerous papers studied on the effects of alkaloids upon the blood picture, RECANI et al.²⁹⁾(1950) pointed out the possible application of epinephrine administration as an activity test of the pituitary-adrenal system according to the observations of VOGT⁴²⁾(1944) and LONG and his associates (1945-1952), since a characteristic decrease of eosinophils, considered to be due to the activation of the pituitary gland, was observed after the administration of epinephrine.

With regard to the effects of atropine on the pituitary-adrenal system, SELYE³⁵⁾(1937) pointed out an unspecific hypertrophy of the adrenals following atropine administration, while VOGT⁴²⁾(1944) described no increase of biocorticoids contents in the adrenal vein blood in the case of atropine administration. However, DORDORI⁶⁾(1950) reported a significant decrease of the ascorbic acid contents in the adrenal cortex of the rat when atropine was administered intraperitoneally, at a dose level of 20 mg per 100 gm of body weight.

The authors performed an experiment on the dog to investigate the effects of atropine, at the level of approximately 0.05 mg per Kg of body weight, which was usually employed for the premedication prior to the general anesthesia. Atropine at this level did not exert any significant effect on the organism, but when a relatively small dose of atropine, 1 mg per Kg of body weight, was injected subcutaneously, changes in the blood picture were very similar to those shown in case of epinephrine administration. It is likely that atropine stimulates the pituitary-adrenal system of the dog unspecifically.

MATERIALS AND METHODS

Adult healthy mongrel dogs, kept under constant environmental conditions, were used.

ACTH*, diluted at a rate of 10 mg in 1 c.c. of normal saline, was administered to 18 dogs intramuscularly, in doses of 0.94 to 2.74 mg per Kg of body weight (15 mg to 14 dogs, 20 mg to 3 dogs, and 25 mg to a single dog). Epinephrine chloride, 1:1000, was injected, subcutaneously, in the amount of 1 c.c. to 10 dogs, and 0.7 c.c. to 4 dogs, while 0.1% solution of atropine sulfate at the dose of 0.05, 0.1, 0.3 and 1 mg, respectively, per Kg of body weight was also injected subcutaneously.

Hemoglobin content was determined by the oxyhemoglobin method. Total white blood count was made in 4 counting chambers (Spencer model) in the usual manner. The blood smears were stained with GIEMSA'S stain and 400 leukocytes were counted. An additional count of eosinophils was made on the same blood samples by RANDOLPH'S chamber method, because it was indicated by RANDOLPH^{27, 28)}, RUD³⁰⁾, SPEIRS and MEYER³⁸⁾ and BEST et al.³⁾ that absolute eosinophil counts were simple to do and much more accurate than the differential countings of eosinophils on a stained blood smear. The modification of RANDOLPH'S staining fluid we used contained equal parts of 0.2% phloxine and 0.1% methylene blue in propylene glycol. It seems to be necessary, in the case of the dog, to double the content of phloxine in the solution, since the eosinophils of the dog are not so easily stained with phloxine as those of other animals. Two Fuchs-Rosenthal counting chambers were used. Blood glucose was determined by the method of Hagedorn-Jensen.

Examinations were made over a period of 6 hours after administration of the agents on the fresh blood samples taken from the cephalic vein of the dog. When a dog was used repeatedly during the experiments, intervals of 10 or more days were taken, since BEST et al.²⁾ indicated a tendency to the diminishing of response in the second test to ACTH, epinephrine, and ephedrine, if performed within 3 days of the previous one.

RESULTS

(A) Diurnal fluctuation

It was emphasized that a pronounced decrease in the number of circulating eosinophils in mice and rats was produced by the excitement due to handling and bleeding. At 4 hours after such excitement was given, SPEIRS and MEYER³⁸⁾ reported a 99% decrease, SPEIRS⁴⁰⁾ a 83% decrease in mice and RECENT et al.²⁹⁾ a 78% decrease in rats. ESSELIER et al.⁷⁾, however, did not observe a significant influence on the blood picture due to such handling and bleeding in guinea pigs.

RUD³⁰⁾ has demonstrated also that eosinophil counts on the blood samples from the same person, taken several minutes apart, may show a greater variation than can be attributed to the intrinsic errors in the counting alone. In addition to this short-time fluctuation, there was a definite diurnal trend, with an average midmorning fall of about 20% below the 8 a.m. level, and a night time peak of about 30% above. HALBERG et al.¹²⁾ reported a diurnal fluctuation in mice.

Moreover, BONNER⁵⁾ stated that fasting alone will cause a drop in the number

*) ACTHAR, Armour products.

**) Adrenalin, Sankyo products.

Fig. 1. Diurnal fluctuation of blood picture in the dog (% changes in 6 dogs)

Fig. 2. Blood picture of the dog following single administration of ACTH (% changes in 18 dogs)

of circulating eosinophils, and since it has been demonstrated that even in nonfasting subjects, the eosinophils drop fairly consistently in the forenoon and rise later in the afternoon, it is felt that the Thorn test may be more sensitive as an index of adrenal responsiveness if done on a nonfasting subject from 1 p. m. to 5 p. m.

The dogs used in this experiment were not given food after 6 p. m. of the previous day. In addition, an experiment was carried out to study in more detail the actual changes in the blood picture in the case of the hour determination which was made over a period of 6 hours, started at 10 to 11 a. m.

As shown in Fig. 1, the results obtained revealed an influence of a slight degree of restraint, bleeding and fasting on the blood picture of the dog.

(B) ACTH

The changes in the hemoglobin contents were very slight following a single administration of ACTH. (Fig. 2).

RECANT reported a 66% increase in the total number of leukocytes, a 67% decrease of the eosinophils and a 60% decrease of the lymphocytes at 4 hours when 15 mg of ACTH was injected to normal dogs intramuscularly. However, the total leukocyte counts, estimated in this experiment, showed a 20 to 30% increase during the period of 2 to 6 hours after injection. The major factor of the increase was the rise in the neutrophil count, as shown in a 78% increase at 4 hours particularly, of the rod-shaped cells, which was revealed from the differential countings on the stained smears of the blood.

The results of the absolute eosinophil count were in gross agreement with the differential countings on the smear. The average count showed a decrease of 54% at 4 hours and 42% at 6 hours. A maximal fall was seen at 4 hours in 10 dogs and at 5 hours in 6 dogs, after which the counts shifted to the increase.

The differences between the counts at 5 hours and those at 4 hours were very small in the cases which showed the maximal fall at 5 hours. Two dogs gave a minimum reading at 6 hours. Eight hour readings determined in 2 other dogs showed higher counts than those at 6 hours. The rate of the eosinophil fall was not dependent upon the initial counts.

Out of 4 dogs administered 15 mg and 20 or 25 mg of ACTH on separate days, 3 dogs showed a marked decrease of the eosinophils through the administration of the larger doses, but in the case of the remaining one, the results were on the contrary.

Merely a relative decrease in the lymphocyte count was observed but absolute lymphopenia was not apparent.

The blood sugar level did not show a remarkable change.

(C) Epinephrine

RECANT reported an eosinophil fall of 50% at 4 hours when 0.2 mg of epinephrine was injected intravenously over a one hour period and, also, when 0.3 to 1 mg of it was injected subcutaneously, to normal dogs.

In this experiment, a slight fall in the total white cell count was observed at 2 hours, but an increase of about 24% at 4 and 6 hours was apparent, while the decrease in the eosinophil count was 52% at 4 hours, and 64% at 6 hours. The neutrophils showed a remarkable increase, while the absolute decrease of the lymphocyte count was 50% at 4 hours and 32% at 6 hours (Fig. 3).

Three of four dogs administered 0.7 and 1.0 mg of epinephrine on separate days, showed slightly marked eosinophil fall following administration of the larger dose, but the remaining one showed an opposite result.

Changes in the hemoglobin contents were not observed.

The blood sugar level showed a pronounced rise due to glycogenolysis.

(D) Atropine

Although there were no significant changes observed after subcutaneous administration of 0.05, 0.1 and 0.3 mg of atropine per Kg of body weight, the injection of 1 mg per Kg of atropine sulfate gave rise to a remarkable change in the white cells in 8 dogs.

The changes were similar to those in the case of epinephrine administration mentioned above, including neutrophilia, eosinopenia and lymphopenia (Fig. 4).

The total white cell counts disclosed an increase of 32% at 4 hours and 37% at 6 hours caused, mainly, by the increase of neutrophils, which was 78% at 4 hours and 76% at 6 hours.

Absolute eosinophil counts revealed a decrease of 53% at 4 hours and 62% at 6 hours. These figures of the eosinophil fall were identical with those in the case of epinephrine administration.

Fig. 3 Blood picture of the dog following single administration of epinephrine (% changes in 14 dogs)

Fig. 4 Blood picture of the dog following single administration of 1 mg per kg. of atropine (% changes in 8 dogs)

The lymphocyte counts showed an absolute decrease of 30% at 4 hours and 17% at 6 hours.

The hemoglobin contents manifested a slight rise.

The blood sugar level showed a rise of 10% at 2 hours.

In 7 dogs on which the effects of ACTH, epinephrine and atropine were tested comparatively on separate days, the responses of the white cells were essentially similar in many respects.

DISCUSSION

There were objections to the reliability of the eosinophil counting method as a measurement of the adrenal cortical activity. Those objections were presented, in particular, as to the evaluation of the epinephrine test on the activity of the pituitary-adrenal system. FORTIER⁸⁾, SPEIRS & MEYER^{38, 39)}, GORDON¹¹⁾ and many other authors described a significant decrease of eosinophils in the hypophysectomized or adrenalectomized animals following epinephrine administration. LOHMEYER¹⁸⁾ and MUEHRCKE et al.²⁵⁾ indicated an indefinite compatibility of the results of the epinephrine test with the hypophyseal-adrenal insufficiencies. ISHIBASHI¹⁶⁾ reported a pronounced eosinopenia after administering Neocyancor, a dye sensitive to the infrared ray, whereas there was no increase observed in the chemocorticoids contents of the adrenal vein blood.

However, it is generally considered that an eosinophil fall following ACTH

Fig. 5 % changes of the blood sugar level in the dog.

administration is produced under the influences of glucocorticoids (glucocorticoid eosinopenia). Recently there appeared works which indicated an intimate interrelation between the eosinophil count and the 17-hydroxycorticoids contents in the circulating blood, since the latter could be measured accurately.

BONDY⁴⁾ and FRANKSSON⁹⁾ indicated it in the case of patients subjected to surgical operations. SHIBUSAWA et al.³⁷⁾ recognized it in the combustion of the dog. It would not be an exaggeration to say that the rise and fall of the eosinophil count in the circulating blood corresponds well enough to the activity of the adrenal

cortex, as the 17-hydroxycorticoids level in the blood is said to represent most precisely the adrenal cortical activity.

It was observed, in this experiment, that the changes in the blood picture were not so obvious following intramuscular administration of ACTH to the dog, as reported by other investigators. On the other hand, BEST²⁾ reported one-sixth of non-Addisonian subjects showed less than a 40% eosinopenia to corticotropin. In 16 of the 18 dogs administered ACTH, the eosinophil fall reached 40% or more. However, the average fall of the eosinophils was 54% at 4 hours and 42% at 6 hours. The maximum fall was seen at 4 or 5 hours, in most cases, and the eosinophil count shifted to the increase thereafter. Absolute lymphopenia and hyperglycemia were not obvious. These relatively small changes shown in the results would be attributed to a short duration of the effects of the agent on the adrenals, in the extent of the doses employed in this experiment, in view of a remarkable decrease of eosinophils at 7 hours following the administration of ACTH gel in a gelatin vehicle to the dog (MARTIN et al.²²⁾).

Several hypotheses have been brought forth to explain the changes in the blood picture following the administration of alkaloids: the acceleration or prevention of the releases of blood cells from the stimulated bone marrow or plain muscles, distributional changes within the blood depots in the body, the stimulation of hemopoiesis. It is generally recognized that the blood corpuscles are under control of the central autonomic nervous system. Although those influences were once recognized, however, the blood picture was not fully explained by the influences of the automototropic agents alone, and any other factors were considered to be^{26, 32)}. The uncertainty of antagonism between the sympathetic and parasympathetic nervous systems shown on the blood picture^{10, 15, 24, 26, 33)} and the opposite responses of the neutrophils and eosinophils, both produced in the bone marrows, to the effects of the agents, seem to suggest the presence of some factors other than the control of the autonomic nervous system.

Although it was indicated by many authors that epinephrine and atropine

produced similar effects on the blood picture, the effects of pilocarpine on it were not very obvious^{1, 34, 26, 32}). PORT and BRUNOW²⁶) observed lymphopenia and eosinopenia or aneosinophilia in all cases with administration of any one of the sympathicotrophic substances (epinephrine, morphine), parasympathicotrophic substances (pilocarpine, choline, veratrine, atropine) or poisons (arsenic), and suggested the effects of some decomposed substances, produced probably during intermediate processes of protein metabolism, not the direct influences of the agents on the autonomic nervous system.

The selective participation of epinephrine in the release of ACTH from the pituitary gland was studied in detail by Long and his associates^{19, 20, 21, 23}) and a hypothesis has been established on the physiological dosage of epinephrine activating the release of ACTH from the anterior pituitary directly or through the hypothalamus. Criticism has been raised, however, to this hypothesis from the experimental and clinical fields, and consequently to the reliability of the epinephrine test as an activity test of the adrenal cortex. On the other hand, ISHIBASHI¹⁶) insisted upon a possible participation of epinephrine in some part of the releasing process of adrenal cortical hormone.

BERTELLI et al.¹) and PORT and BRUNOW reported a pronounced eosinopenia and neutrophilia following administration of atropine. The dosage of atropine employed by PORT and BRUNOW was 0.7 or 0.8 mg. per Kg. in the dog. VOGT denied the correlation of atropine with the pituitary-adrenal system in the dog. However, SELYE³⁵) described the correlation in young rats and DORDORI pointed out a significant fall of the adrenal ascorbic acid concentration following atropine administration, at a dose of 20 mg per 100 gm of body weight and proposed the possibility of precluding a cholinergic control of ACTH release. SAWYER and PARKERSON³¹) reported the presence of the adrenergic mediators in the mechanism of ACTH release as recognized in the mechanism of LH release. KOBAYASHI¹⁷) revealed an augmentation of eosinopenia following administration of adrenal cortical extracts by pretreatment of atropine.

The resemblance of the effects of atropine, administered at a dosage of 1 mg per Kg., on the blood picture with those of ACTH and epinephrine seems to suggest that atropine may not affect the regulation of the blood picture directly as an autonomic agent, but present the pronounced changes in the blood picture by accelerating the secretion of adrenal cortical hormone as a result of its participation into the pituitary-adrenal system as a nonspecific stimulant.

The deduction will be endorsed by further experiments, to be conducted by these authors¹⁴) on an interference of pentobarbital anesthesia with the effects of atropine on the blood picture.

SUMMARY

A study was made on the effects of ACTH, epinephrine and atropine upon the blood picture of the dog. The responses of the white blood cells to these agents are essentially similar in many respects.

ACTH, administered intramuscularly in doses of 15 to 25 mg., induces a marked eosinopenia (-54%) and neutrophilia ($+79\%$) at 4 hours, while the subcutaneous

administration of epinephrine, in doses of 0.7 to 1.0 cc, and atropine, at the level of 1 mg per Kg, respectively, brings about a pronounced eosinopenia, lymphopenia and neutrophilia at 4 to 6 hours. The decrease in the eosinophil count is 52% at 4 hours and 64% at 6 hours after epinephrine, and 53% at 4 hours and 62% at 6 hours after atropine.

On the other hand, the influences of restraint, bleeding and fasting of the dog on its blood picture are very little and the diurnal fluctuation in the blood picture is not obvious.

In view of works reported by many authors which indicate the uncertainty of antagonism between the sympathetic and parasympathetic nervous systems shown on the blood picture, the opposite responses of the neutrophils and eosinophils to the effects of the agents, the possibility of precluding a cholinergic control of ACTH release and the presence of the adrenergic mediators in ACTH release, atropine, at a level of 1 mg per Kg of body weight, is considered to act by itself as a non-specific alarming stimulus, exerting the effects on the pituitary-adrenal system of the dog. But, at the level of pre-anesthetic medication, the agent has no significant influences on the animal.

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犬の血液像に対する ACTH, エピネフリン及び アトロピンの影響

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生体に非特異的な侵襲が加へられると汎適応症候群が発現し、その警戒反応の時期に特徴ある血液像の変化すなわち好酸球の減少、淋巴球の相対的又は絶対的減少及び好中球の増加と主として後者に基く白血球総数の増加が生ずることは SELYE によって指摘された。THORN は ACTH の投与によつて起る顕著な好酸球減少反応が副腎皮質機能の判定に役立つことを報告し (Thorn test), さらに RECENT は VOGT 及び LONG らの成績にもとづいてエピネフリンの投与によつて発現する好酸球減少反応は下垂体副腎皮質系の機能判定法として用いられると述べている。

副腎皮質からの Glucocorticoids 分泌が亢進することによって流血中の好酸球数が減少すること (Glucocorticoid Eosinopenia) は今日一般に認められているが、下垂体副腎皮質系の機能判定法としての Epinephrine test についてはかなりの疑義が提出されている。しかしエピネフリンが副腎皮質ホルモンの分泌に関与していることは否定できないと考えられている。

副腎皮質機能の検査法のひとつとして用いられている好酸球数算定法については近時流血中好酸球数と 17-hydroxycorticoids 含量との相反する態度を裏付ける BONDY, FRANKSSON, 渋沢らの成績が発

表されている。今回の実験に於てはすべて RANDOLPH 法に従つて好酸球数の直接算定を行つたが、犬の好酸球顆粒は他の動物に比して染色されにくいので稀釈液中のフロキシンの濃度は原法の 2 倍とした。

著者らは犬に対する ACTH (15~25 mg, 筋肉内 1 回注射) およびエピネフリン (1,000 倍液, 0.7~1.0 cc, 1 回皮下注射) の効果を追試して、すでに発表されている多くの報告と同様の成績を得たが、さらに全身麻酔の前麻酔薬としてモルヒネ, ナルコポン, オビスタンなどと併用されているアトロピンが生体に与へる影響を検討した。

その結果、前麻酔の際に適用されているアトロピンの用量 0.05 mg/kg では血液像に認むべき変化は生じないが、投与量を 1 mg/kg に増した場合に於て前記のエピネフリン投与の場合とほぼ一致して、注射後 4 および 6 時間に顕著な好酸球減少、淋巴球減少及び好中球の増加とこれにもとづく白血球総数の増加の起ることを認めた。

マウスおよびラットでは血液像に日差が見られること、また保定、採血などの操作によつて著しい好酸球減少の起ることが知られており、モルモットではこのストレス反応が生じないと報告されているが、正常犬について検査した結果では、1 時間々隔

で7回の採血を行ったが血液像の変動は軽微にとどまりストレス反応は見られなかった。

アトロピンと副腎皮質との関連について、VOGTは副腎静脈中の biocorticoids を測定した結果これを否定しているが、SELYEはアトロピン注射によつて非特異的に副腎の肥大が生ずることを報じ、DORDORIはラットにアトロピン 20 mg/100 gm, B. W. を投与すると副腎皮質のアスコルビン酸含量が著減することからこれを示唆している。また古く BERTELLI らおよび PORT & BRUNOW は犬に於てアトロピン投与による顕著な好酸球減少および好中球増加を認めている。

血液像の形成が自律神経系の支配をうけていることは一般に認められているが、アルカロイドの血液像に対する影響を検討した多くの成績は必ずしも一致せず、血液像形成に対する交感神経毒と副交感神経毒との間の拮抗関係についてはこれを肯定するものと否定するものがあり、またピロカルピンの効果には一定の傾向が認められていない。また同じく骨髓組織で作られる好中球と好酸球の相反する態度については十分に説明されていない。PORT &

BRUNOW は交感神経毒(アドレナリン, モルヒネ), 副交感神経毒(ピロカルピン, コリン, ヴェラトリン, アトロピン)および毒(砒素)のいずれによつても好酸球の減少又は消失および淋巴球減少が起ることから, これはこれらの薬物の自律神経系に対する直接的作用によつて発現するものではなく, 恐らく蛋白質のある種の間代謝産物の作用によるものであると推定した。

著者らは以上の諸説及び ACTH の分泌には cholinergic control が存在しないとする DORDORI および ACTH 分泌には adrenergic mediators が存在するとする SAWYER & PARKERSON の成績から, 1 mg/kg のアトロピンの皮下投与によつて犬に発現したエピネフリン投与時と酷似した白血球の変化は, アトロピンが非特異的な刺激のひとつとして下垂体副腎皮質系に感作した結果と考へる。この見解はペントバルビタール前処置が ACTH, エピネフリンおよびアトロピンの効果に及ぼす影響に関する次回の報告によつて裏付けられると考へるものである。