PHYSIOLOGY

THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN REGULATING THE MORPHOLOGICAL COMPOSITION AND QUANTITY OF HEMOGLOBIN IN PERIPHERAL BLOOD

II. The Effect of Pain Stimulation and Adrenalin Injections on the Blood Pattern of Dogs With A Damaged Thalamic-Hypothalamic Region

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(Received August 23, 1954. Presented by Active Member of the Academy of Medical Sciences of the USSR V. N. Chernigovsky.)

We are interested in the problem of the role which the thalamic-hypothalamic region plays in regulating blood changes and the process of blood formation after pain stimulation and adrenalin injection were applied to the animal.

Experiments were carried out on dogs with unilateral and bilateral damage to the thalamic-hypothalamic region and on dogs with unilateral damage in this region and an additional two-stage removal of the cortex of the cerebral hemispheres.

The present discussion concerns the effect of pain stimulation and adrenalin injection on the blood pattern in dogs with a damaged thalamic-hypothalamic region.

EXPERIMENTAL METHOD

The primary unilateral injury of the thalamic-hypothalamic region was produced in 14 dogs (with a weight of 7 to 19 kg), of which 8 survived. Seven months prior to the injury of the thalamic-hypothalamic region, the solar plexus of one of the dogs (No. 25) was destroyed, and five months prior to the destruction of the hypothalamic region the rear half of the spinal cord was cut at vertebrae C_3-C_4. All the other dogs were subjected to a two-stage removal of the cortex of the cerebral hemisphere.

An instrument (Fig. 1) specially designed in the laboratory under the direction of E. A. Asratyan was used to damage the thalamic-hypothalamic region; it was a straight metal tube – cannula (inside diameter 2 mm, outside diameter 2.5 mm, length 11 cm) which was inserted through a metal disk containing a set screw (a).

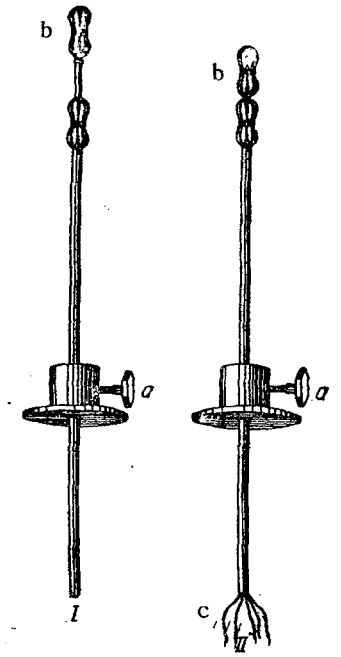

Figure 1. Apparatus used in impairment of thalamic-hypothalamic region. Description in text.

The screw permitted the disk to be fixed at various heights, and thus to vary the length of the inserted portion of the cannula. A metallic mandrin with a cap was located within the cannula (b). On the end of the mandrin were fastened 5-6 metallic wires. When the mandrin rises, the wires come together in the hollow of the cannula, and when it descends they emerge from the cannula in an umbrella-shaped pattern (c). Piercing the cerebrum and withdrawing the cannula is effected in Position I. The cannula is bored into the brain to the desired depth. Then the mandrin cap is pushed down, causing the cannula which lies in the brain to assume Position II. After attaining this position, the mandrin is energetically turned around a longitudinal axis (to the right and to the left), destroying the specific area of the brain. Then the mandrin is raised to its former position (Position I), and the cannula withdrawn. In such an operation bleeding is usually not very profuse because the blood coagulates quickly. The method of pain stimulation was described in Communication I [1]. The adrenalin solution (1 : 1000) was administered by means of hypodermic injection in doses of 0.15 mg for each kg of animal weight.

In all, 9 experiments were performed on 5 dogs with damaged thalamic-hypothalamic regions (Fig. 2); 5 experiments were conducted on 4 dogs with pain stimulation and 4 experiments with adrenalin injections.

RESULTS OF EXPERIMENTS

As can be seen from the data of Table 1, a 3 to 5 minute electrical stimulation of the skin of the lower third of the rear extremities caused a diminution in all the dogs of the quantity of erythrocytes, hemoglobin and thrombocytes per unit volume of peripheral blood.

On the average the quantities of erythrocytes was 7% less than normal in 10-15 minutes; 5.8% less than normal at the end of 25-30 minutes, and the quantity of erythrocytes had returned to normal after 40-45 minutes. The hemoglobin content had decreased by 3% in 10-15 minutes after stimulation, 7.6% after 20-25 minutes, and 6% after 40-45 minutes.

Along with the diminution of the quantity of erythrocytes, stimulation by pain caused in all dogs a "paradoxical" increase of the volume index. No particular regularity was noted in the dynamics of fluctuations in the quantity of reticulocytes.

The number of thrombocytes decreased an average of 18% within 10-15 minutes after stimulation by pain; within 25 to 30 minutes, however, it returned to normal.

In all dogs, with the exception of No. 74, within 25 to 30 minutes after pain stimulation a marked increase was noted in the quantity of leucocytes.

Comparing the blood pattern changes caused by pain stimulation of dogs subjected to unilateral damage to the thalamic-hypothalamic region, and the blood pattern changes of the control group dogs, we see that while in the latter group pain stimulation causes marked increase in the quantity of erythrocytes, hemoglobin and thrombocytes in the peripheral blood, and in the majority of cases the decrease of the number of leucocytes, the stimulation of dogs with injured thalamic-hypothalamic regions causes the opposite effect in the majority

of cases; i.e., diminution of the quantity of erythrocytes, hemoglobin, and thrombocytes, and an increase in the number of leucocytes.

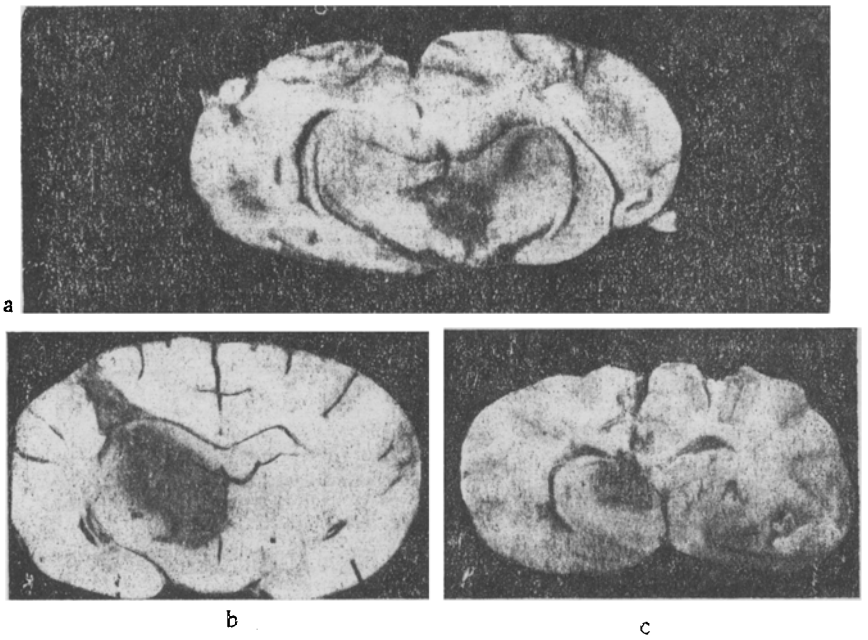

Figure 2. Region of impairment of the thalamic-hypothalamic region in dog No. 68, which died on 8th day after the operation (a); dog No. 55 which died on the 5th day (b); dog No. 25 which died on the 6th day (c) (the impairment was performed in two stages: it was begun on the right side and completed on the left side within 35 days).

In contrast to pain stimulation, adrenalin injection in a majority of cases resulted in an increase of the quantity of erythrocytes and hemoglobin in the peripheral blood, which was maintained after the injection for a period of 25 to 30 minutes or longer (Table 2). The increase in the number of leucocytes and the volume index of the blood was particularly marked.

As with pain stimulation, the quantity of thrombocytes and reticulocytes decreases in a majority of cases after adrenalin injections.

The ability of adrenalin to produce a more pronounced effect on the blood pattern in terms of an increase in the quantity of the regular blood cells and hemoglobin, as compared to the pattern which is obtained after pain stimulation, probably depends on the capacity of adrenalin to excite directly the vasomotor and sympathetic centers of the brain and spinal cord, as well as to excite the more peripherally situated tissues. On the other hand, in order to attain the autonomic effects produced by pain stimulation, the entire thalamic-hypothalamic region must be intact, since the basic reflex arcs of pain sensitivity join there.

The difference in the effects of pain stimulation and adrenalin injections is clearly shown in the study of the rhythm of the heart-beat and respiration. Pain stimulation caused a significant reduction of the number of cardiac systoles and respiratory movements. The degree and duration of this reduction varied with different dogs, and was dependent to a definite degree upon the time elapsed after the operations.

In the case of four dogs, the number of cardiac systoles decreased, on the average, from 119 to 93 per minute immediately after pain stimulation, while respiratory movements decreased from 21 to 15 per minute. Restoration of the heart rhythm came within 20-25 minutes, and of respiration within 30-40 minutes, after pain stimulation (Table 3).

TABLE 1

Blood Patterm of Dogs With a Bilateral Impairment of the Thalamic-Hypothalamic Region Before and After a 3-5 Minute Application of Pain With An Electric Current in the Lower Third of the Rear Extremity.

No. of dog	Sex	Weight (in kilograms)	Date of experiment	No. of days after operations	Prior to pain stimulation							Within 10-15 minutes after pain stimulation						
					erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in $^0/_{00}$)	thrombocytes (in thousands)	leucocytes (in thousands)	erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in $^0/_{00}$)	thrombocytes (in thousands)	leucocytes (in thousands)
74	male	12.6	20 Dec.'51	11	6,950	70	0.5	0.63	2	240	15.2	5,380	66	0.56	0.66	7	230	14
75	female	12.5	20 Dec.	17	4,700	62	0.65	0.5	2	220	9.0	4,460	60	0.67	0.61	1	180	13.2
58	female	6.4	28 June	30	4,650	66	0.7	—	—	300	13.4	4,380	69	0.78	—	—	150	15.4
70	male	9.8	15 Nov.	45	5,580	65	0.58	0.47	25	250	16.4	5,700	62	0.52	0.5	16	270	16.0
Average					5,170	66	0.61	0.53	10	252	13.5	5,105	64	0.63	0.59	8	207	14.6

Continuation

No. of dog	Sex	Weight (in kilograms)	Date of experiment	No. of days after operation	After pain stimulation													
					Within 25-30 minutes							Within 40-45 minutes						
					erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in $^0/_{00}$)	thrombocytes (in thousands)	leucocytes (in thousands)	erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in $^0/_{00}$)	thrombocytes (in thousands)	leucocytes (in thousands)
74	male	12.6	20 Dec.'50	11	7,450	63	0.42	0.69	4	210	11.2	7,020	64	0.45	—	—	450	10.6
75	female	12.5	20 Dec.	17	4,710	60	0.63	0.47	1	230	11.6	4,350	63	0.63	—	—	170	10.6
58	female	6.4	28 June	30	4,290	62	0.7	—	—	250	16	—	—	—	—	—	—	—
70	male	9.8	15 Nov.	45	4,580	58	0.63	0.53	12	400	20	4,570	60	0.64	—	—	260	17.2
Average					5,257	61	0.59	0.56	5.7	272	14.7	5,180	62	0.57	—	—	293	12.9

Note: Volumetric index computed from data obtained from use of a hematocrite.

TABLE 2

Blood Patterns Before and After Subcutaneous Injections of Dogs with a Bilateral Injury of the Thalamic-Hypothalamic Region

No. of dog	Sex	Weight (in kilograms)	Date of experiment	No. of days after operation	Prior to adrenalin injections							Within 10-15 minutes after injection of adrenalin						
					erythrocytes (in millions)	hemoglobin (%)	color index	volume index	reticulocytes (in ‰)	thrombocytes (in thousands)	leucocytes (in thousands)	erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in ‰)	thrombocytes (in thousands)	leucocytes (in thousands)
74	male	12.6	20 Dec. '51	18	6.300	64	0.5	0.66	6	250	8.4	6.400	70	0.55	0.85	8	220	16
75	female	12.5	20 Dec.	18	5.510	65	0.58	1.1	4	260	9.8	4.970	60	0.76	—	1	240	10.9
69	female	9.1	15 Nov.	43	5.680	70	0.6	0.82	4	245	8.4	6.800	72	0.53	0.82	7	480	10.2
70	male	9.8	15 Nov.	50	5.100	61	0.59	—	10	300	17.4	4.780	61	0.63	—	5	230	—
Average					5.647	65	0.57	0.86	6	263	11	5.713	66	0.61	0.84	5	292	12.4

Continuation

No. of dog	Sex	Weight (in kilograms)	Date of experiment	No. of days after operation	erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in ‰)	thrombocytes (in thousands)	leucocytes (in thousands)	erythrocytes (in millions)	hemoglobin (by %)	color index	volume index	reticulocytes (in ‰)	thrombocytes (in thousands)	leucocytes (in thousands)
74	male	12.6	20 Dec. '51	18	6.970	65	0.46	0.92	9	310	8.0	6.370	70	0.52	—	—	350	10.8
75	female	12.5	20 Dec.	18	4.310	60	0.62	1.2	4	230	11.0	5.020	61	0.60	—	—	180	8.2
69	female	9.1	15 Nov.	43	5.400	68	0.63	1	8	340	8.8	-	—	—	—	—	—	—
70	male	2.3	15 Nov.	50	5.250	63	0.6	—	10	130	20	4.200	60	0.71	—	—	350	18
Average					5.557	64	0.58	1.06	8	252	12.2	—	—	—	—	—	—	—

Note: The volume index of erythrocytes in dogs No. 69 and 75 was determined on the basis of characteristics obtained after centrifugation of the blood, which was preserved in citrate. The volume index of dogs No. 70 and 74 was computed on the basis of data obtained from use of a hematocrite.

TABLE 3

Change in the Rate of Cardiac Systoles and Respiratory Movements Before and After Pain Stimulation and Adrenalin Injections of Dogs With A Unilateral Impairment Of The Thalamic-Hypothalamic Region.

No. of dog	Date of Experiment	Day after operation	Prior to application of pain and adrenalin		After application of pain and adrenalin									
					Immediately afterwards		Within 5 minutes		Within 10 minutes		Within 20 minutes		Within 30 to 40 minutes	
			Pulse	Respiration	Pulse	Respiration	Pulse	Respiration	Pulse	Respiration	Pulse	Respiration	Pulse	Respiration
			In minutes											
			Pain stimulation											
74	20 Dec. 1951	11th	96	28	66	22	64	26	66	28	83	–	96	–
75	20 Dec.	17th	76	12	82	15	86	13	82	14	89	14	108	14
58	27 July	30th	152	20	80	7	104	10	110	13	152	15	–	–
70	31 Dec.	45th	152	22	144	18	160	18	150	20	180	22	18	21
			Adrenalin injections											
74	8 Jan. 1952	18th	115	22	140	33	160	36	160	–	144	32	152	34
75	8 Jan.	18th	96	16	–	–	86	17	106	28	125	25	130	22
70	5 Jan.	51st	160	22	146	28	132	28	225	40	220	32	152	32
69	12 Jan.	57th	126	20	142	28	154	32	160	36	142	30	132	26

In contrast to pain stimulation, adrenalin injections produced in all dogs, independently of the time elapsed after the operation, a significant increase of systolic and respiratory frequency.

The maximum increase of heart rhythm occurred within 10 minutes after the injection; the number of systoles increased, on an average, from 124 to 163 a minute, and did not return to normal for a period of 30-40 minutes.

An increase of respiratory frequency was noted immediately after the adrenalin injection. It reached its maximum within 10 minutes, and did not return to its original level until 30-40 minutes after the injection.

Pain stimulation, inflicted upon dog No. 25 on the fifth day after the supplementary operation, which consisted of damage to the left thalamic-hypothalamic region (35 days prior to this operation, the right thalamic-hypothalamic region was injured), did not cause a marked change in the circulatory system.

Before pain stimulation dog No. 25 had 5,170,000 erythrocytes, 10,000 leucocytes, 0.2% reticulocytes and 66% hemoglobin. Immediately after a 3 minute application of pain, these properties of the blood changed in the following manner: the number of erythrocytes was reduced to 5,140,000, the number of leucocytes increased to 12,000, the number of reticulocytes fell to 0.1% and the quantity of hemoglobin was reduced to 64%. Within 15 minutes after the stimulation the respective figures were: 5,030,000, 16,000, 0.2% and 62%. Consequently, only an insignificant increase in the number of leucocytes can be noted after the stimulation.

The absence of any noticeable effect of pain stimulation on the blood pattern of dog No. 25 (which has a bilateral damage of the thalamic-hypothalamic region) is evidently associated with a complete loss of nociperception.

The dog was observed for a length of time after the operation. During the post-operative observation period the dog was in a continuous deep stupor and did not respond to electrical stimulus of the skin on the shank and head.

The observed changes in the cellular composition of the peripheral blood, and rhythm of the heart and respiration after pain stimulation of dogs with a damaged thalamic-hypothalamic region indicate the important physiological significance of this part of the brain in achieving the pressor effect of pain stimulation on the peripheral blood pattern and the activity of the cardiovascular and respiratory mechanisms.

The enrichment of the peripheral blood with its regular blood cells and hemoglobin, as well as the increased frequency of heart beat and respiration which occur after violent stimulation have been applied are directed toward assuring the ability of the defensive mechanism of the organism to operate. On the other hand, in dogs with a damaged thalamic-hypothalamic region, these changes assume a completely opposite character. This indicates the important part which this region plays in the mobilization of the autonomic components and their activation in the defense mechanism of the organism.

It is doubtful however, whether it would be correct to assume that the absence of enriched blood with its regular blood cells and hemoglobin and the abrupt retardation of the heart rhythm and respiration after pain stimulation in dogs with a damaged thalamic-hypothalamic region is completely due to the impaired activity of the damaged section of the brain.

The gross operative damage of the thalmus-hypothalamus also involves the damaging of numerous afferential and efferential nerve passages which originate in various parts of the central nervous system and pass through this region. The operation also damages those reflex arcs which join here.

The damaged thalamic-hypothalamic region can become the seat of impulses differing in the character and intensity of impulses. These impulses can cause a temporary reduction in the excitability of different parts of the brain, particularly the cortex of the dominant hemisphere (negative induction). Therefore, the distorted reaction of the blood, heart rhythm and respiration after pain stimulation of the dogs being experimented on must be considered as a consequence of the impaired perception of

pain impulses on the part of the thalamus-hypothalamus and other regions of the brain and spinal cord.

Damage to the thalamic-hypothalamic region causes a strong inhibition of the sympathetic nervous system. The parasympathetic nervous system is evidently little affected by it. This is shown by the pronounced retardation of the heart rhythm and respiration in addition to a significant protraction of the state of general inhibition of these animals after pain stimulation.

Pain stimulation inflicted on dogs with a damaged thalamic-hypothalamic region causes a protracted state of general inhibition (semi-conscious state) lasting 30-50 minutes and longer. This condition is not found in normal animals and especially in dogs deprived of the cortex of both hemispheres. The impairment of thermo regulation of these dogs also indicates the depressed functioning of the sympathetic nervous system. When the room temperature was lowered to an insignificant extent (12-14°) they began to shiver heavily. Inasmuch as the stimulation of the hypothalamic region causes an intensified secretion of adrenalin [2], it may be assumed that damage to this region must cause the opposite effect produced, i.e., a decrease of the adrenalin secretion.

The absence of enriched peripheral blood enriched by cellular elements and hemoglobin, in addition to retardation of heart beat and respiration upon application of pain stimulation to animals is evidently related in many ways to the depression of the sympathetic adrenalin system, which occurs after impairment of the thalamic-hypothalamic region.

Freedom from hyperadrenalemia which is found in dogs with an injured thalamic-hypothalamic region after the application of pain stimulation is indicated by the enrichment of the blood with its cellular elements and by a considerable increase of heart beat frequency and respiration after adrenalin injections.

The difference between the effects produced by pain stimulation and adrenalin injection are evidently due to the direct effect of adrenalin on the vasomotor and respiratory centers. On the other hand, in order for pain stimulation to have an effect it is necessary for the reflex arcs which join in the thalamic-hypothalamic region to be intact. It is possible that the impairment of the thalamus-hypothalamus causes a temporary increase in the sensitivity of the cardiovascular system, respiratory mechanism, and the organs of the heart to adrenalin, as is noted with respect to the denerved structures.

LITERATURE CITED

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