ELECTROENCEPHALOGRAPHIC STUDIES OF ANTIPYRETIC ANALGESICS

REPORT 2. THE EFFECT OF AMINOPYRINE ON THE RABBIT

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The mechanism of action of the antipyretic drugs has been discussed from the point of view based mainly on the hypothalamic thermoregulatory center. Since the introduction of Mayer's classical theory (1), many authors (2-6) have attributed the site of action of the drugs to the hypothalamus and other basal nuclei from their extensive studies. In the previous paper the author has studied on the effects of aminopyrine on the electroencephalogram in cats (7). The results that the manifestation of the seizure discharge of the spontaneous EEG in cat in response to aminopyrine was preceded by the manifestation of the seizure discharge or spike waves of the hypothalamic and thalamic EEG have suggested the primary site of action of aminopyrine on the diffuse region of the anterior hypothalamus.

However, the electrophysiological studies of aminopyrine by Fujita *et al.* (8, 9) have shown the diffuse dimensions of the site of action within the brain. The effects of aminopyrine shown by the authors, according to the general consideration, may include various aspects of the drug effects such as analgesic, antipyretic and other side effects as well as the secondary or rebound effects. In the current report attempts were made to differentiate the unique antipyretic effect of aminopyrine from the other effects either dependent or independent on the antipyresis by comparing the time course of the EEG changes.

Moreover, the effects of aminopyrine on the EEG were also studied in the rabbit which had received the pyretic doses of 2,4-dinitrophenol.

METHODS

The experiments were performed on male rabbits weighing 2.4 to 3.2 kg. After the insertion of the tracheal cannula the animals were fixed on the stereotaxic instrument (Todai Noken Type), and their skulls were trephined under ether anesthesia. In order to avoid the effect coming from the operative procedures measurement of the body temperature and the EEG recording were started two hours, thereafter.

Recording of the EEG from the motor cortex was carried out monopolarly by use

of the silver electrode and the indifferent electrode was located on the frontal bone closely to the frontal sinus. The dental broaches, insulated except of their tips and separated each other at the distance of 2 mm, were used as the stimulating electrode for the midbrain reticular formation as well as the centre médian nucleus of the thalamus.

The stimulator used was a type of MSE-3, and the isolator used was a type of MSE-Jm (Nippon Kodens Co. Ltd.). In the early parts of the experiments the 2-channel universal recorder of Type-MPA-204 was used for the recording of EEG. However, in the later parts the 12-channel encephalograph of the Type-BK-129 (San'ei Instrument Co. Ltd.) which had the time constant of 0.3 was used. For the analysis of the frequency of the EEG the analyser of Type-EA-101 (San'ei Instrument Co. Ltd.) furnished with 2-4, 4-8, 8-15, 15-30, 30-60, 60-100 and 100-150 c/sec wave-band pass filters and the 10 seconds integrator were used.

Respiratory movements and EKG (II induction) were occasionally recorded at the time constant of 1.5 together with the EEG recording.

Rectal temperature was measured by use of the thermister mounted on the catheter and placed at the depth of 6 cm from the sphincter ring. To avoid the effects of the mechanical damage of the brain on the body temperature, the rectal temperature was not measured in the animals on which the subcortical electrodes were inserted.

Five percent of aminopyrine in the doses of 25 to 150 mg/kg was administered into the marginal ear-vein at the intervals of 2 to 5 minutes. The rise of the body temperature was obtained by the subcutaneous injection of 1% 2,4-dinitrophenol in the dose of 15 mg/kg dissolved in 1% Na_2CO_3 (10) to the back of the animal.

The experiments were performed at the room temperature of 20-24°C, and the special care was taken to avoid the external noise stimuli which might affect the EEG.

RESULTS

I. Chronological Changes of Body Temperature after the Fixation

Soon after the fixation, anesthesia and trepanation the rectal temperature showed a trend of gradual decline and the steady temperature was attained about two to three hours, thereafter. The body temperature in the steady state showed a mean value of 37.7°C and ranged from 34.7°C to 40.7°C at the 95% rejection limit. The change of the rectal temperature from the mean after the administration of aminopyrine within the 95% rejection limit was regarded as normal, that of the temperature within the limit of 95-99% as moderately elevated (+) or lowered (-), that of the temperature above the limit of 99% rejection as strongly elevated (++) or lowered (---). The results are shown in Fig. 1.

II. Effects of Aminopyrine on the Spontaneous EEG

The doses of aminopyrine used were 25, 50, 70-75, 100 and 150 mg/kg. The characteristic effect of aminopyrine on the spontaneous EEG was the manifestation of the slow

FIG. 1. The time course (180 minutes) of the mean body temperature in 11 rabbits after the steady level of the body temperature was attained.

waves associated with or without the preceding seizure discharges (Figs. 2 and 3). These slow waves intermingled with few spindle burst activities manifested persistently for 10 to 30 minutes after the injection, and the integrated values of the EEG frequency analyser for every 10 seconds showed the predominant increase of the 2-4 c/sec-band (the first substages). However, thereafter, the spontaneous EEG shifted to the increased manifestation of the spindle burst-like activities, and the integrated value of the EEG frequency analyser showed the marked increase of the 8-15 c/sec-band (Fig. 2). The spindle burst-like waves, frequently mixed with the arousal waves recovered to the EEG patterns of the normal period before one to two hours after the administration of aminopyrine. Though these seizure discharges of the EEG occurred often repeatedly every 1 to 3 minutes in some of the animals, they were usually not observed in response to slower speed of injection of aminopyrine even in larger doses. The results are shown in Tables 1-4.

For the further elucidation of the relation of the EEG changes and the fall of the body temperature produced by aminopyrine the author presented the following hypotheses, derived from the results described above. Though the hypotheses were examined by χ^2 -test, the dose-response effects were neglected. The hypothesis 1 consisted in the possibility that the fall of the body temperature associated with the manifestation of the slow waves in the spontaneous EEG. As is shown in Table 2-A and B, the possibility could not be rejected with 5% of significance, and moreover it proved being more significant in one group of animals in response to one dose (25 mg/kg). The hypothesis 2 consisted in the possibility that the elevated body temperature associated with the elicitation of the seizure discharges. As is shown in Table 3, the possibility could not be rejected with 5% of significance. The hypothesis 3 consisted in the possibility that the fall of the body temperature associated with the arousal pattern of the spontaneous EEG which manifested one hour after the administration of amino-

FIG. 2. The slow wave pattern of the EEG in the motor cortex induced by 50 mg/kg of aminopyrine in rabbit (MC_1 and MC_2) and its momentary and integrated values of the frequency analyser.

Arrows in the Figs. 2 and 3 indicate the spindle burst activity.

Pen deflections of the integrator from the left indicate the integrated values of 2-4 c/sec, 4-8 c/sec, 8-15 c/sec, 15-30 c/sec, 30-60 c/sec, 60-100 c/sec and 100-150 c/sec band.

Resp. means the respiratory curve.

pyrine. The third possibility could be rejected with 5% of significance, as is shown in Table 4.

III. Reticular Arousal Response during the Manifestation of the Slow Waves induced by Aminopyrine

As is shown in Fig. 4, the 8-15 c/sec-band activity in the spontaneous EEG was depressed moderately by stimulation of the brain-stem reticular formation with the

FIG. 3. The EEG during control period and seizure discharge elicited by the administration of 50 mg/kg aminopyrine.

This and the next figures are traced because the vagueness of the original pictures.

intensity of 3.5 volts (Notice the records in Fig. 4-B and C that the integrated values of the frequency analyser traced just one phase prior to the corresponding pattern of the EEG (10 sec, 15 cm), because the integrator pen traveled always 30 cm behind the EEG recording and the paper speed was set at 1.5 cm/sec.

The 8-15 c/sec-band activity ($\downarrow$) and 2-4 c/sec-band activity ($+$) of the spontaneous EEG were not markedly depressed ($\downarrow\downarrow$ and $++$, respectively) by 50 mg/kg of aminopyrine which definitely evoked the manifestation of the slow waves. The result seemed to show some elevation of the threshold for the reticular arousal response by the dose of aminopyrine.

IV. Recruiting Response during the Manifestation of the Slow Waves induced by Aminopyrine

The centre médian nucleus of the thalamus was stimulated with the stimuli 4.2 volts in intensity, 8 c/sec in frequency and 1 msec in duration. The intensity of the stimuli was quite similar to the threshold voltages required to obtain the recruiting response before the administration of drugs. The recruiting response was enhanced 5 minutes after the injection of 50 mg/kg of aminopyrine, while it was depressed slightly at 30 minutes and almost fully recovered at 45 minutes after the injection.

The time course of the threshold variation, that is, the threshold lowering in the first slow wave sub-stage and the threshold elevation in the second slow wave sub-stage seemed to be the reflection of the background changes of the spontaneous EEG,

TABLE 1. Effect of aminopyrine on the rabbit.

Control			After intravenous administration						
No.	EEG	Temperature (°C)	EEG			Temperature (°C)			
			Seizure	Slow wave	1hr	15m	30m	60m	90m
25 mg/kg									
I	1 a	39.0	—	—	a	o	o	o	o
I	2 m	37.1	—	—	a	o	o	o	o
I	3 a	38.7	—	+	a	—	—	o	o
I	4 m	38.3	—	+	a+sl	—	—	o	o
I	5 m	37.6	—	—	m	o	o	o	o
50 mg/kg									
II	1 m	37.0	+	+	m+sl	o	o	o	o
II	2 m	37.6	+	+	m	o	o	o	o
II	3 m	37.0	+	+	m+sl	o	o	o	o
II	4 m	37.7	—	+	m+sl	—	—	o	o
II	5 m	38.4	—	+	m+sl	—	—	o	o
II	6 m	39.3	+	+	a	+	o	o	o
II	7 m	38.9	—	+	m+sl	+	o	—	o
70-75 mg/kg									
III	1 a	38.4	—	+	a	—	—	o	o
III	2 m	35.8	+	+	a+sl	+	+	o	o
III	3 m	36.8	+	+	a+sl	++	—	—	—
III	4 m	39.4	+	+	m	++	++	+	+
III	5 m	38.8	—	—	m	+	+	+	+
100 mg/kg									
IV	1 a	39.1	—	—	a	o	o	o	o
IV	2 a	35.3	+	+	a+sl	—	—	o	o
IV	3 m	37.6	+	+	m+sl	+	o	o	o
IV	4 a	39.1	—	+	a	—	—	—	—
IV	5 a	38.3	+	+	a	+	+	o	o
IV	6 a	38.5	+	+	a	+	—	—	—
IV	7 a	39.0	—	+	a	—	—	—	—
150 mg/kg									
V	1 a	39.2	+	+	a+sl	++	o	—	—
V	2 m	37.5	—	+	a+sl?	—	—	—	—

Symbols of "a", "m" and "sl" in the table mean the arousal pattern, mixed pattern and slow wave (*See text*).

The mixed pattern followed by Kikuchi's definition (11).

TABLE 2(A). The 2×2 contingency table of the relationship between the body temperature and slow wave induction in the animals in the different dosages group.

		Slow wave		Total
		+	—	
Body temperature (30-60 min after administration)	Lowered	13	0	13
	Elevated and invariable	8	5	13
	Total	21	5	26

TABLE 2(B). The 2×2 contingency table of the relationship between the body temperature and slow wave induction in the same dosage group (25 mg/kg).

		Slow wave		Total
		+	-	
Body temperature (30-60 min after administration)	Lowered	2	0	2
	Elevated and invariable	0	3	3
	Total	2	3	5

TABLE 3. The 2×2 contingency table of the relationship between the body temperature and elicitation of seizure discharge.

		Seizure discharge		Total
		+	-	
Body temperature (15 min after administration)	Lowered and invariable	4	12	16
	Elevated	8	2	10
	Total	12	14	26

TABLE 4. The 2×2 contingency table of the relationship between the body temperature and appearance of arousal pattern of EEG 1 hour after aminopyrine administration (Cases in which "a" is assigned in the control period are excluded).

		Arousal pattern of EEG		Total
		+	-	
Body temperature (60 min after administration)	Lowered	2	1	3
	Elevated and invariable	3	10	13
	Total	5	11	16

These results suggested the possibilities that there was some interaction of the activities between the background cortical EEG and the recruiting response or some filtering effects of the subcortical activity on the cortical pattern of EEG.

V. Effect of Aminopyrine on the Respiratory Frequency

The administration of the moderate doses of aminopyrine elicited tachypnoea which persisted for 30 minutes to two hours. The typical cases are shown in Figs. 6 and 7. In Fig. 6, the respiratory frequencies before the injection of aminopyrine were 42-48/min. When the aminopyrine was injected, the respiratory frequency was increased up to over 90/min. This high increase was always associate with the manifestation of seizure discharges in the EEG and recovered gradually to the normal level within 30 minutes after the injection. The manifestation of the slow waves in the EEG which lasted during period of the increased respiratory frequency turned to that of the slow waves intervened by the intermittent arousal waves, thereafter.

There was a clear-cut difference in the respiratory frequency between these two types of the EEG pattern. In the slow wave stage of the EEG the respiratory frequency was usually less than 55/min, while in the arousal wave stage it was more than 55/min. The results suggested some relation between the mode of the EEG pattern and

FIG. 4. Reticular arousal responses produced by repetitive stimulation (3.5V in intensity, 300 c/sec in frequency and 1 msec in duration) of the brain-stem reticular formation.

Reticular arousal responses during control period and 5 min, 30 min and 60 min after aminopyrine in the dose of 50 mg/kg are recorded on the motor cortex (MC) and hippocampus (HPC).

The hippocampal EEG during stimulation was not shown because of large shock artifact.

Pen deflections of integrator are the same as that of Fig. 3.

As the signs ($\downarrow$, $\downarrow\downarrow$, $+$, $++$), see the text.

the activity of the respiratory center. Fig. 7 shows the case in which the respiratory frequency increased considerably in accord with the spontaneous manifestation of the slow waves but without the manifestation of the seizure discharges in the EEG in response to 70 mg/kg of aminopyrine. The results suggested that the moderate increase of the respiratory frequency substantially followed to the manifestation of the slow waves in the EEG, and that the strong increase of the respiratory frequency obtained during the slow wave stage immediately after the manifestation of the seizure discharges was likely to be derived from the after-effects of the seizure.

VI. Effects of Aminopyrine on the Heart Rate

The heart rate of the fixed animal was usually in the range of 38 to 46/10 sec. During the manifestation of the seizure discharges induced by aminopyrine the rate

FIG. 5. Recruiting response produced by repetitive stimulation (4.2 V in intensity, 8 c/sec in frequency and 1 msec in duration) of the centre médian nucleus of the thalamus. Momentary analysis of the cortical EEG is also shown (8-15 c/sec).

FIG. 6. Time course of respiratory frequency change after 50 mg/kg aminopyrine administration (i.v.).

FIG. 7. Time course of respiratory frequency change after 50 mg/kg aminopyrine i.v. administration (No seizure discharge was elicited). The signs are the same as that of Fig. 6.

was increased up to 50 to 70/10 sec for about one minute, and thereafter it decreased abruptly to the level of 18 to 40/10 sec. The decreased rate lasted for 5 to 30 minutes and recovered gradually. The tachycardia was sometimes observed in the later period of aminopyrine action when the spontaneous EEG showed mixed type of patterns. The two types of the responses of the heart rate to aminopyrine are shown in Figs. 8 and 9. The one was the case which showed the manifestation of the seizure discharges in the EEG (Fig. 8), and the other was the case which did not respond because of the slow injection of aminopyrine (Fig. 9). The initial manifestation of the bradycardia was observed in the latter animal. It was unlikely that the heart rate differed significantly according to the pattern of the EEG.

As was described above, the slow wave pattern of the EEG induced by the injection of aminopyrine could be classified into the following two stages, i.e., the initial depressed and the late recovery substages regarding the activities of the 8-15 c/sec-band of the EEG frequency analyser. In order to obtain some correlation between the level of the

FIG. 8. Time course of heart rate change after 100 mg/kg aminopyrine i.v. administration.

FIG. 9. Time course of heart rate change after 50 mg/kg aminopyrine i.v. administration (because of the slower injection the seizure discharge was not elicited). (Δ : Length of pen-deflection of 8-15 c/sec activity in arbitrary scales. Other signs are the same as that of Fig. 8).

bradycardia and the level of the depression of 8-15 c/sec-band frequency the time course of both effects of aminopyrine were compared, as is shown in Fig. 10. Though the recovery of the bradycardia (13 to 17 minutes) followed that of 8-15 c/sec-band activity (11 to 15 minutes), they trended differently thereafter.

As is shown in Table 5, the comparative measurement of the time-length needed for 50 beats of the heart and the extents of the pen-deflection for the integrated recording of the 2-4 c/sec- and 8-15 c/sec-band of the EEG in a centimeter scale showed that the EEG did not respond to 25 mg/kg of aminopyrine significantly, while the heart rate changed significantly. The result seemed to be another evidence supporting the independent character of the heart rate on the EEG change.

VII. Effects of Aminopyrine on the Febrile Rabbit in Response to 2,4-Dinitrophenol

It has been postulated that though the antipyretics such as aminopyrine lowers the body temperature of the febrile animals, it does not affect the normal temperature

FIG. 10. Solid line : Five terms moving averages of the length of 10 heart beats.
Dotted line : That of the height of pen-deflection of 8-15 c/sec in arbitral scale.

TABLE 5.

	Control	25 mg/kg aminopyrine administration (after 5-15 min)
2-4 c/sec	33±10.5	31±5.6
8-15 c/sec	18.2±3.85	18.6±3.95
50 heart rate (each 30 samples)	2.78±0.15	3.12±0.09

unless the excessive doses is given (5). Narusawa (12), in this laboratory, has shown that Irgapyrine, the derivative of aminopyrine, lowered the body temperature of the febrile rabbit administered 2,4-dinitrophenol previously. As is shown in Figs. 12 and 13, the administration of aminopyrine to the animal given 15 mg/kg of 2,4-dinitrophenol previously induced the similar manifestation of the seizure discharges and the slow waves of the EEG as that of aminopyrine in the normal animal. It was pretty difficult to obtain a clear-cut effects of aminopyrine on the EEG because of the overlapping of the slow waves induced by 2,4-dinitrophenol with those induced by aminopyrine.

FIG. 11. Time course of body temperature after 15 mg/kg dinitrophenol s.c. administration.
Each point represents the mean body temperature $\pm$ standard errors of 11 rabbits.

FIG. 12. Time course of body temperature with the standard point 1.5 hours after 15 mg/kg dinitrophenol s.c. administration.

FIG. 13. Time course of body temperature with the standard point 1.5 hours after 15 mg/kg dinitrophenol s.c. administration.

Moreover, there were two cases which worthed to mention. The one was the case in which the lowering of the body temperature was observed during the manifestation of the slow waves of the EEG, and another was the case in which the rise of the body temperature was observed during the manifestation of the seizure discharges of the EEG (case No. 3 in Fig. 13). Any remarkable difference of the effects of aminopyrine neither on the body temperature nor the other behaviours was detected irrespective of the previous administration of 2,4-dinitrophenol.

DISCUSSION

The assumption that the aminopyrine-induced EEG changes were the reflection of the various effects of the drug, that is, antipyretic, analgesic and some side effects, the secondary responses to its proper effects, etc. promoted the current experiments to elucidate the detailed mode of action of aminopyrine on the spontaneous EEG. Firstly, attempts were made to classify the EEG patterns produced by aminopyrine into groups according to the wave frequency. Analysis of the slow wave patterns of the EEG induced by aminopyrine by means of EEG frequency analyser differentiated the following two substages. The first substage consisted of the increased activity of 2-4 c/sec- and 8-15 c/sec-band. Following the first substage the second substage in which the increased activity of the 8-15 c/sec-band intermingled with the modulated spindles and

the occasional arousal waves was observed.

The results obtained from the present experiments that the reticular arousal responses were depressed by aminopyrine in either substages indicate the central depressant effect of the drug. The same conclusion was presented by many authors (13-15) concerning other central nervous system depressants. On the other hand, the recruiting response was enhanced by aminopyrine in the first substage, while it was depressed in the second substage. A similar biphasic effect of phenobarbital on the recruiting response has been reported (16).

The biphasic effects of aminopyrine on the recruiting response suggest that the site of action diffusely extends from the midbrain reticular formation to the diffuse thalamic projection system.

The model diagram, shown in Fig. 14, will contribute appreciably to correlate the

FIG. 14.

manifestation of the slow waves of the EEG with the antipyretic action of aminopyrine or to show the possibility that the slow wave pattern induced by aminopyrine is a real measure of the central, especially antipyretic effects.

The body temperature is usually determined by the differential activity of the heat production and heat dissipation of the effector organs within the body.

Barbour (5) has mentioned that the thermostat mechanism set at higher level of activity in fever, and that though the normal body temperature is interpreted as cold, the elevated temperature such as 40°C is interpreted as neutral by the temperature regulating center. The similar suggestion has been presented by von Euler *et al.* (17). They have explained the effects of adrenaline and noradrenaline on the thermoregulatory mechanism from the point of view of the threshold raiser of the heat center or of a threshold lowerer of cold center. Antipyretics such as aminopyrine may be a threshold raiser of heat center or threshold lowerer of cold center according to the dual heat center theory of Hans Meyer (1). The explanation that the antipyretics is a threshold lowerer of cold center is quite favorable to apply for the results previously reported by the author (7).

The assumption that the heat loss center in the hypothalamus activated by aminopyrine may feel the normal body temperature relatively warm allows the manifestation of, at least, two kinds of response train according to the degree of the body temperature:

1) the synchronization of cortical EEG, cutaneous vasodilatation, inhibition of gamma motor activity (18), and inhibition of respiratory frequency (19), 2) the desynchronization of cortical EEG, cutaneous vasoconstriction, acceleration of gamma motor activity, panting (18), bradycardia (20), etc.

However, the effects of aminopyrine on the spontaneous EEG, respiratory frequency and heart rate obtained from the present experiment are contradictory to the hypothetical response trains described above. There were the decrease of the heart rate induced by the smallest dose of aminopyrine, the moderate increase of the respiratory frequencies as well as the concomitant changes of the EEG induced by the increasing doses of the drug, and neither the demonstration of the decrease of the respiratory frequencies nor panting even in large doses of the drug. These evidences as well as the effects of aminopyrine on the heart rate shown in Figs. 9 and 10 strongly suggest that the bradycardia manifests independently from the initiating mechanism of the slow waves of the EEG, and therefore, the bradycardia may derive from the peripheral effect of aminopyrine or from some unknown effect on the subcortical structures.

It may be reasonable to consider that bradycardia contribute in some part, to the antipyretic effect through the calorogenic inhibition. On the contrary, the slow wave pattern of the EEG corresponds directly to the activity of the respiratory center, as is shown in Fig. 7. The correspondence may show that the slow wave pattern is induced by the excitation of the respiratory center or *vice versa*, although some other unknown factors responsible for the correspondence could not be excluded from the present results.

There is no possibility of close correlation between the respiratory frequency and the thermoregulatory mechanism. However, the increased respiratory frequency which have been reported being proportional to the oxygen consumption (21), accelerate naturally the heat production, while the excessively increased respiratory frequency accelerates the heat dissipation *via* evaporation (22). These assumption may indicate that the balancing mechanism of the respiratory frequency responsible for the elevation of the lowering of the body temperature is working always in the body. The moderate increase of the respiratory frequency is likely being profitable for the elevation of the body temperature.

The statistical χ^2 -test proves a significant correlation between aminopyrine induced slow wave and the fall of the body temperature. The elevation of the body temperature associated with the manifestation of the seizure discharge in the EEG may sometimes mask the antipyretic effect of aminopyrine, and therefore, some animals which received aminopyrine may not exhibit antipyretic response.

The results in the present experiments that the moderate increase of the respiratory frequency associated with the lowering of the body temperature was observed in the slow wave stage of the EEG seem contradictory to the above-mentioned references. For the elucidation of the lowering mechanism of the body temperature in this case further studies, for instance, regarding to the secondary effect of aminopyrine on the

heat dissipation should be needed.

The cutaneous vasodilatation in the rabbit's ear in response to aminopyrine was reported by Morita (23). Though the vasomotor activity of the ear vessels in the rabbit has been reported to play an important role to regulate the body temperature (24, 25) Morita could not offer any evidence that the antipyretic effect of aminopyrine derived from the vasomotor activity alone. The postulations, obtained from the present experiments, that the slow wave pattern of the EEG induced by aminopyrine is useful for a measure of the temperature-threshold change in the thermoregulatory center or of the secondary effect of the drug on the heat dissipation may contribute to explain Morita's results to some extent.

Studies on the mode of action of the analgesics on the evoked potentials in the anesthetized animals by Fujita *et al.* (8) have shown some effects of aminopyrine which were quite different from those of morphine and other narcotic drugs.

The characteristic effects of aminopyrine are the enhancement of the activity of the intracortical neurons, the facilitation of the corticofugal impulse transmission from the brain-stem, etc. These effects may be the reflection on the respiratory, thermoregulatory and possibly other autonomic responses to aminopyrine.

On the other hand, the different effects of aminopyrine on the normal and the febrile body temperature seem to be explained by the quantitative term rather than the qualitative one and could or could not be explained by the hypothesis that in the febrile state the threshold lowering mechanism is activated by the administration of aminopyrine.

Further studies should be needed to elucidate the mechanism of antipyretic effect of aminopyrine including the more quantitative study of the activities of the effector organs (output in Fig. 14) which affect the thermoregulatory mechanism and the EEG.

SUMMARY

The effects of aminopyrine in the dose range of 25 to 150 mg/kg on the EEG, body temperature, respiratory frequency and heart rate were studied in the restrained but unanesthetized rabbits.

1. The administration of aminopyrine induced the manifestation of the slow waves in the EEG preceded sometimes by the seizure discharges. The integrated values of the EEG frequency analyser classified the period of the slow wave into two substages. The arousal waves were sometimes appeared in the second substage.

2. The reticular arousal response was depressed during the appearance of the slow waves, while the recruiting response was enhanced in the first substage and depressed in the second one.

3. The respiratory frequency was strongly increased during the seizure discharge or the arousal pattern of EEG, while it was moderately increased in the slow-wave stage.

4. The heart rate was initially increased during the seizure discharge, and then

decreased during the slow-wave stage; it was also decreased transiently neither when the seizure discharge nor the slow waves was elicited. The heart rate change was considered as independent of EEG change.

5. The effect of aminopyrine was observed in febrile rabbit injected 15 mg/kg of 2,4-dinitrophenol. No qualitative difference could be found between normal and febrile rabbits.

6. The central and peripheral action mechanisms of aminopyrine antipyresis were discussed with reference to "aminopyrine-induced slow wave."

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