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GAMMA AMINOBUTYRIC ACID: CIRCULATORY AND RESPIRATORY EFFECTS IN DIFFERENT SPECIES; RE-INVESTIGATION OF THE ANTI-STRYCHNINE ACTION IN MICE

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γ-Aminobutyric acid (GABA) is a normal brain constituent which on topical application to the mammalian cortex inhibits electrically or chemically induced convulsions (Hayashi & Nagai, 1956) and reverses surface negative post-synaptic dendritic potentials of apical dendrites (Purpura, Girado & Grundfest, 1957*a*, *b*; Iwama & Jasper, 1957). The intravenous administration of GABA fails to produce such effects, since GABA does not pass the blood-brain barrier easily (Purpura, Girado, Smith & Gomez, 1958; van Gelder & Elliott, 1958). Thus initial hopes that GABA might be useful in the treatment of epilepsy soon had to be abandoned. However, since in the conscious, healthy man GABA in doses of 50 or 100 mg I.V. produced respiratory discomfort, bradycardia and hypotension, the circulatory and respiratory effects of GABA in anaesthetized common laboratory animals were analysed and the results obtained are reported here. The anti-strychnine action of peripherally administered GABA, described by McLennan (1957), was also re-investigated.

METHODS

To study the effect of γ-aminobutyric acid (GABA) on circulation and respiration, experiments were carried out on dogs weighing 7–15 kg, cats weighing 2–3·5 kg and rabbits weighing 1·5–3 kg. Animals of both sexes were used and all experiments were carried out under anaesthesia. Unless otherwise stated the following procedure was used. Dogs received an I.V. injection of sodium thiopentone 5–15 mg/kg and additional small doses of sodium thiopentone were given whenever required; throughout each experiment a state of surgical anaesthesia was maintained and GABA was injected into a superficial vein of a forelimb. Rabbits were anaesthetized with 1–2 g urethane I.V.; further doses of urethane were given whenever required and GABA was injected into the

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marginal ear vein. Cats were anaesthetized with chloralose 70–80 mg/kg I.V., and GABA was injected into the femoral vein.

The blood pressure was recorded on a smoked drum via a mercury manometer connected to a cannula inserted into the left common carotid artery of cat or rabbit and the left femoral artery of dog. In some dogs the blood pressure was recorded with a Statham pressure transducer, Model P 23 A, connected to a Sanborn strain gauge amplifier equipped with writing pen. To avoid blood clotting, 1000 i.u. heparin was injected into the arterial cannula immediately after its insertion.

Respiration was recorded with a volume recorder fitted with an adjustable leak and attached to the expiratory side of a two-way valve system, which was fitted to the tracheal cannula.

Counts of the heart rate were made from graphic records of the electrocardiogram, which was registered with a Sanborn electrocardiograph using bipolar chest–limb leads for animals and bipolar peripheral leads for human subjects.

Intracisternal injections were given via a cannula, the tip of which was located in the cisterna magna. After withdrawal of 0·2 ml. of cerebrospinal fluid, a syringe containing 0·2 ml. GABA solution was attached to the cannula, 0·2 ml. of cerebrospinal fluid was withdrawn into the syringe and the mixture of GABA solution and cerebrospinal fluid was then injected intracisternally.

Perfusion experiments. The perfusion fluid was a modified Tyrode solution (Hobbiger, 1958*a*) containing (g/100 ml.) NaCl 0·9, KCl 0·02, $CaCl_2$ 0·02, $MgCl_2$ 0·01, $NaHCO_3$ 0·05 and glucose 0·1, equilibrated with 95% N_2 + 5% CO_2 and pre-warmed to 37° C.

For heart perfusions the Langendorff method was used. GABA and other substances were added to the perfusion fluid in a volume of 0·2 ml. by injection with a syringe, the needle point of which was located distally to a partial air gap within the perfusion system. The volume of perfusion fluid in the space between air gap and tip of the perfusion cannula amounted to 3 ml.

For the perfusion of hind limbs animals were killed by decapitation and the body was divided at the level of the diaphragm. An inflow cannula was inserted into the aorta below the level of origin of the renal arteries and the outflow cannula into the abdominal vena cava. The rate of outflow was counted with a Gaddum drop-recorder. GABA was injected directly into the inflow cannula via a two-way connector piece.

For studying the *antistrychnine action* of GABA, white mice of both sexes were used. The mice were either inbred and of an unclassified strain obtained from the Royal Victoria Hospital, Montreal, or of the CF_1 strain obtained commercially.

γ-Aminobutyric acid (Merck or Roche Products Ltd.) is referred to throughout the text as GABA.

RESULTS

Experiments on human subjects

Three healthy male human volunteers were given GABA by injection into the anticubital vein.

One subject received 50 mg and 35 min later a further 100 mg. A few seconds after each injection the electrocardiogram showed a short period of tachycardia followed by a longer-lasting period of bradycardia, followed again by tachycardia (Fig. 1). Attempts were made to measure the pressure in the brachial artery by auscultation during this period, but although a fall of more than 25 mm Hg (from 115 mm Hg) could be established by these means, the change was too abrupt for its maximum or time course to be accurately ascertained. A few seconds after each injection the subject noticed numbness in the limbs, a pricking sensation in the skin, dry mouth, respiratory discomfort, pulsations in the head and a 'rising sensation in the stomach'.

Of the two other volunteers one received a single dose of GABA 5 mg, and the other two doses of GABA 5 mg given at a 5 min interval. A few seconds after the injection both subjects noticed a pricking sensation in the skin and respiratory discomfort, and felt hot and very apprehensive; the e.c.g. showed tachycardia which in the case of the second dose of GABA was preceded by a transient period of bradycardia.

In all three subjects the subjective symptoms completely disappeared within 2–5 min. Five minutes after the injection of GABA the blood pressure was normal but tachycardia disappeared more slowly.

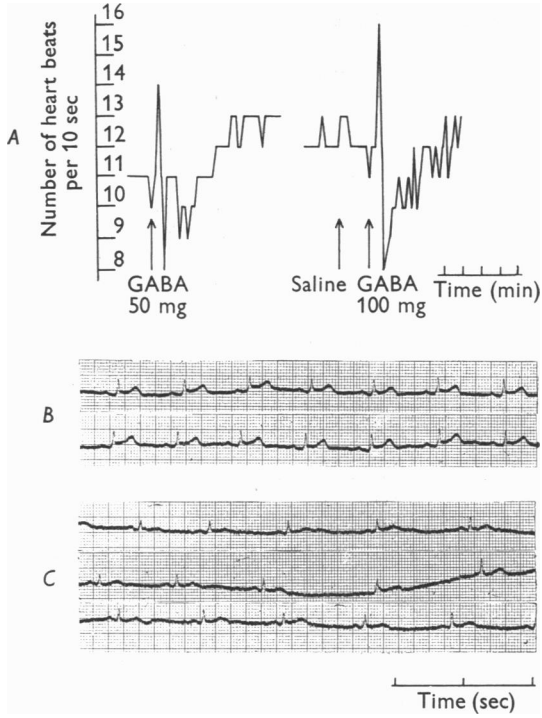

Fig. 1. Effect of GABA I.V. on the heart rate of a human subject. The two graphs labelled *A* show the effect of GABA 50 and 100 mg. The tracings below are records of the e.c.g. The records labelled *B* are two consecutive records showing the e.c.g. before injection, and the records labelled *C* are consecutive records showing the e.c.g. during the period while bradycardia, following the injection of GABA 100 mg, was most pronounced.

Effects of GABA on circulation and respiration in animals

Rabbits

Takahashi, Tiba, Iino & Takayasu (1955) injected GABA into the marginal ear vein of rabbits anaesthetized with urethane, and made the following observations. GABA lowered the blood pressure for a period of a few minutes up to some 10 min, and with any given dose the duration of hypotension was

directly related to the depth of anaesthesia. The hypotensive action began within 10–15 sec of the injection and quickly reached a maximum. The maximum effect obtained with GABA represented a 50–60% fall of the blood pressure. The threshold dose was GABA 0·07 mg/kg, and GABA 10 mg/kg produced either the same or a slightly greater effect than higher doses.

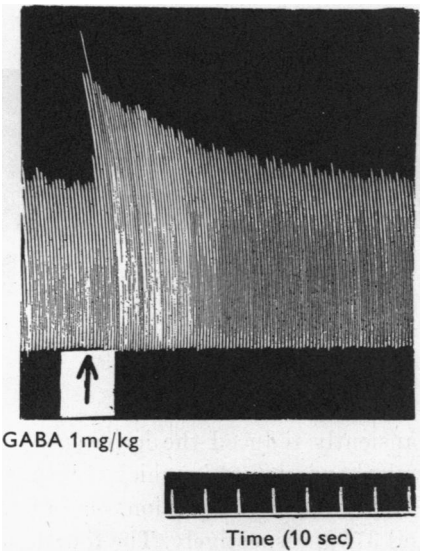

Fig. 2. Records of the respiratory stimulation by GABA I.V. in a rabbit (2·1 kg; urethane anaesthesia). Control injections of saline had no effect on the respiration.

These findings were confirmed in principle in our experiments. Takahashi *et al.* (1955) also stated in their publication that GABA produced bradycardia, but gave no detailed information on it. In our experiments bradycardia was negligible, and even with doses of GABA which were in excess of that required for a maximum hypotensive effect bradycardia never amounted to more than a 10% lengthening of the interval between any two heart beats.

A major discrepancy between our results and those of Takahashi *et al.* (1955) concerns the effect of GABA on respiration. Whereas the Japanese authors state that GABA first depresses respiration and then stimulates it, in our experiments GABA invariably only stimulated respiration. In some experiments the stimulation of respiration was marked (Fig. 2) but in others it was only just noticeable. The respiratory stimulation preceded hypotension by a few seconds and sometimes coincided with a slight rise of the blood pressure.

The following additional observations were made in our studies.

The hypotensive action of GABA is not confined to rabbits under urethane anaesthesia, since it was also observed when sodium thiopentone or chloralose were used as anaesthetic agents. A hypotensive action was obtained regularly

when doses not exceeding 5 mg/kg were given at 30 min intervals (Fig. 3). However, with doses ranging from 1 to 5 mg/kg, the effect of the first injection was usually greater than that of the second injection of the same dose. Subsequent injections produced an effect very similar to that given by the second injection. Doses exceeding 5 mg/kg produced a desensitization to GABA after the blood pressure had returned to its pre-injection level. The degree and duration of desensitization were proportional to the dose of GABA used.

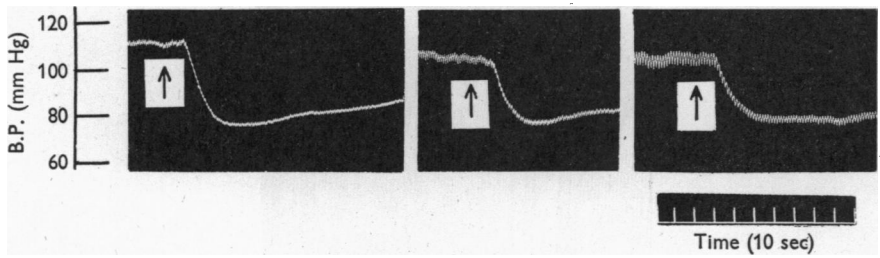

Fig. 3. Records of the circulatory effects of three I.V. injections of GABA 1 mg/kg in a rabbit (1·9 kg; urethane anaesthesia). The injections, indicated by the arrows, were given at intervals of 30 min.

Pentamethonium transiently reduced the hypotensive action of GABA to a small extent. In a typical experiment in which GABA 3 mg/kg was injected at 30 min intervals the second and third injections of GABA lowered the systolic blood pressure by 36 and 37%, respectively. The fourth dose of GABA, given 5 min after an injection of pentamethonium bromide 10 mg/kg, lowered the systolic blood pressure by 28% and the fifth dose by 34%. Neither atropine sulphate in doses of 1 mg/kg nor bilateral vagotomy modified the response to GABA under the same experimental conditions.

Dogs

In dogs GABA I.V. regularly produced hypotension. The hypotension was always transient and its duration was determined by the dose used (Fig. 4). The lowest effective dose of GABA was usually of the order of 0·01–0·02 mg/kg and 1–10 mg/kg invariably produced the same or even a slightly greater effect than higher doses. The maximum fall of systolic blood pressure obtained with GABA in different experiments was 30–40%. Doses of GABA of the order of ten times the threshold dose or higher produced considerable bradycardia, which was most marked while the blood pressure fell or was at its lowest (Fig. 5).

Doses of GABA which lowered the blood pressure also transiently reduced the depth of respiration (Fig. 6). The depression of respiration was always abrupt in onset and during the recovery phase an increase in the rate of respiration was seen in some dogs (Fig. 6).

The delay between injection and onset of respiratory and circulatory actions

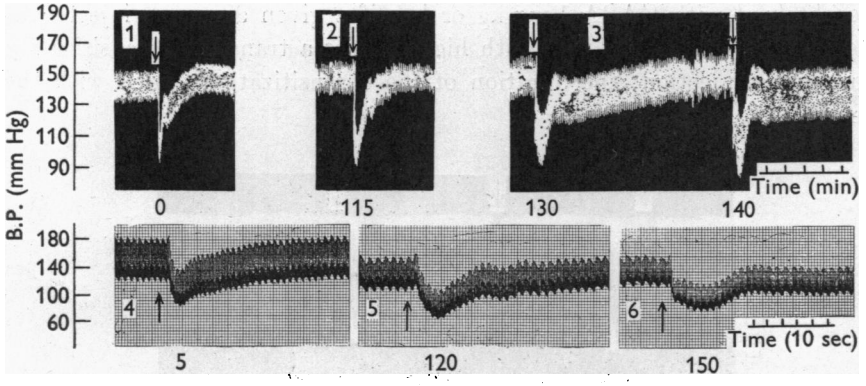

Fig. 4. Circulatory action of GABA I.V. in the dog (15·2 kg; sodium thiopentone anaesthesia). The upper tracings are records obtained with a mercury manometer and the lower tracings are records obtained with strain-gauge recording. Records 1, 2, 4 and 5 show the effect of GABA 0·03 mg/kg, records 3 and 6 show the effect of GABA 0·3 mg/kg. The figures beneath individual records give the time of injection in minutes after the first injection (record 1).

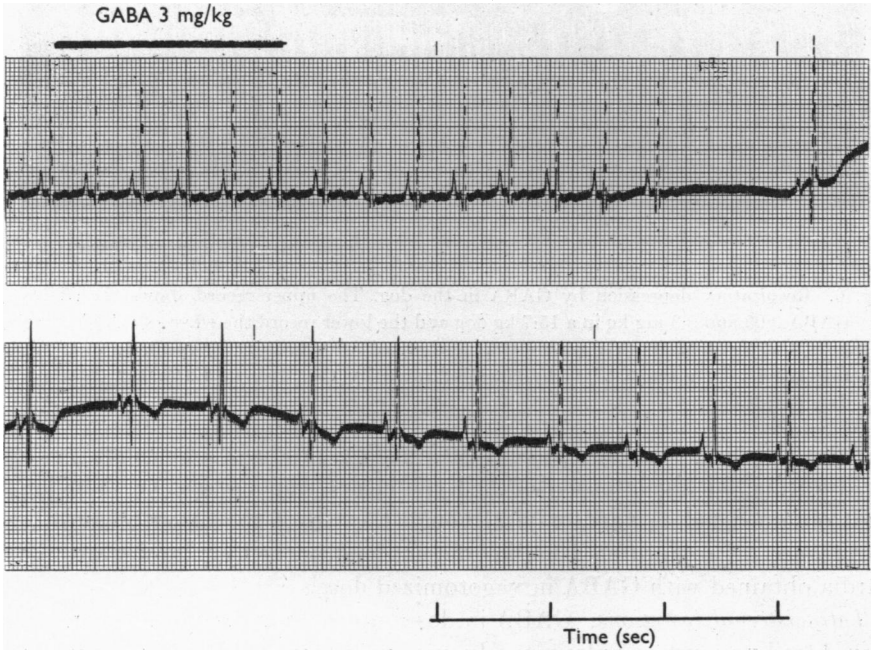

Fig. 5. Electrocardiogram of a dog (10·7 kg; sodium thiopentone anaesthesia) injected with GABA 3 mg/kg I.V. The two records are consecutive tracings.

of GABA varied from 5 to 10 sec in different experiments, and identical effects were obtained with GABA 1 mg/kg or less if a given dose was injected at suitable intervals (Figs. 4, 6). With higher doses a transient desensitization followed the injection; the duration of the desensitization varied with the dose of GABA given.

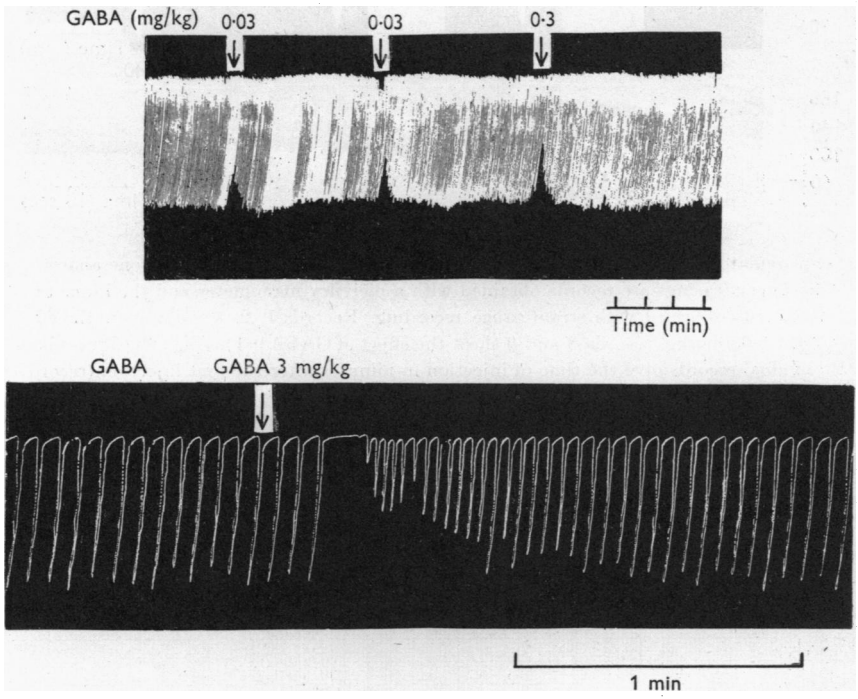

Fig. 6. Respiratory depression by GABA in the dog. The upper record shows the effects of GABA 0·03 and 0·3 mg/kg in a 15·7 kg dog and the lower record the effect of GABA 3 mg/kg in a 10·7 kg dog. Both dogs were anaesthetized with sodium thiopentone and GABA injections were given I.V. at the time indicated by the arrows. Expiration is recorded downwards.

After bilateral vagotomy GABA 1 mg/kg produced considerably less bradycardia, but the intensity of the hypotensive response was very similar to that obtained before vagotomy, although the fall of the blood pressure was less abrupt. Atropine (0·5–1 mg/kg) did not modify the hypotension or bradycardia obtained with GABA in vagotomized dogs.

Intracisternal injections. GABA in doses up to 2 mg did not affect respiration, blood pressure or pulse rate. In one experiment GABA 10 mg depressed the depth of respiration for several minutes and raised the blood pressure considerably for more than 30 min. The interval between injection and the onset of both these effects was of the order of 1–2 min. In a second experiment GABA 20 mg was given and after a 1 min delay respiration gradually ceased

and the blood pressure fell to very low levels while the dog was kept on artificial respiration. It is possible that some of the effects obtained with GABA 10 or 20 mg were caused by the hypertonicity of the injected fluid.

Cats

Chloralose anaesthesia. GABA, given I.V., produced variable effects on the blood pressure. In some experiments GABA lowered the blood pressure whereas in others it produced a hypertensive or a biphasic response (Figs. 7, 8). Hypotensive effects were often preceded by a just noticeable rise of the blood pressure (Fig. 7). The lowest effective dose of GABA varied between 0·1 and 1 mg/kg; 10–100 mg/kg always produced the same or a slightly greater fall of

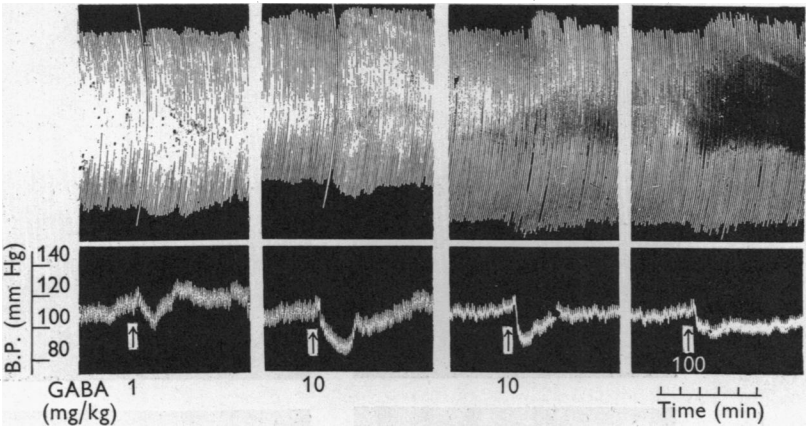

Fig. 7. Circulatory and respiratory effects of GABA I.V. in a 2·5 kg cat, anaesthetized with chloralose. The upper records show respiration, expiration downwards. The lower records show the blood pressure. Injections of GABA were given at 30 min intervals and are indicated by the arrows. The records are superimposed in such a way that the point of maximum expiration is directly above the corresponding point of the blood pressure.

the blood pressure than higher doses. Both hypo- and hypertensive effects started 5–10 sec after the injection and their duration was determined by the dose. The effect of GABA 10 mg/kg on the systolic blood pressure, expressed as a percentage of the blood pressure before the injection of GABA, amounted to -6, -22, <-5, -20, -15, -15, $+6$ and $+15\%$ in different cats. Effects of GABA on the heart rate were negligible. The maximum change recorded in a cat in which GABA produced a hypotensive response amounted to a 20% lengthening of the interval between heart beats during the period while the blood pressure fell.

The respiratory effects of smaller doses of GABA often consisted of a single gasp when the first 1–3 injections were given (Fig. 8) and a slight increase in depth of respiration was frequently seen after higher doses (Fig. 7).

Barbiturate anaesthesia. In five cats anaesthetized with 50 mg sodium pentobarbitone/kg given intraperitoneally, GABA produced transient hypotension, comparable to or smaller than that illustrated in Fig. 7.

Experiments under conditions used in electrophysiological studies. The medial portion of the brain stem was partly coagulated at the level of the superior colliculus on both sides of the mid line (Iwama & Jasper, 1957). Sodium thiopentone anaesthesia was employed before brain stem coagulation and injections of GABA were given several hours later. In two experiments, carried out under these conditions, GABA in doses of 10 and 100 mg/kg slightly raised the systolic blood pressure for periods of less than 30 sec. In a third cat GABA in

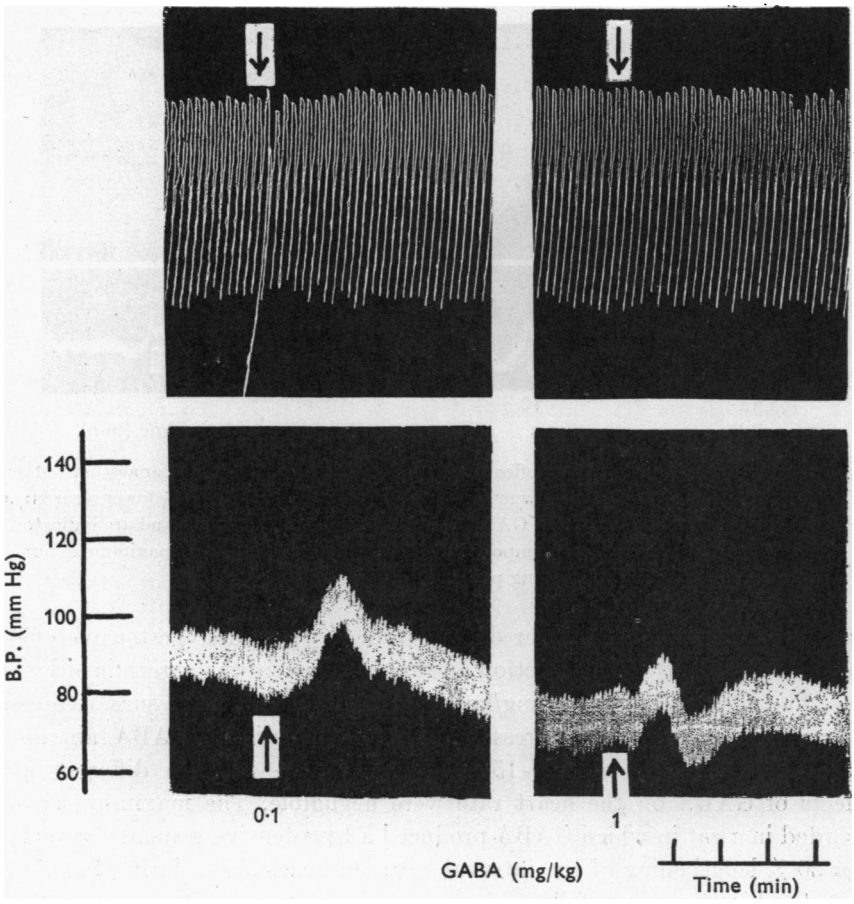

Fig. 8. Circulatory and respiratory effects of GABA I.V. in a 1·9 kg cat, anaesthetized with chloralose. The upper records show the respiration, expiration downwards. The lower records show the blood pressure. Injections of GABA were given at 30 min intervals and are marked by the arrows.

doses of 10 and 100 mg/kg raised the systolic blood pressure for 3–4 min by 18 and 26%, respectively.

Intracisternal injections in cats under chloralose anaesthesia. In three experiments GABA 0·01 and 0·1 mg raised the systolic blood pressure for 30 sec to 2 min by up to 15%. In a fourth experiment GABA 0·1 mg had a small hypotensive effect. GABA 1 mg produced either hypotension or hypertension, or hypertension followed by hypotension. All these effects represented blood pressure changes not exceeding 25% in either direction and lasted for 2–3 min or longer. A second dose of GABA 1 mg had no blood-pressure effect if the cat was artificially respired.

Transient depression of respiration was noticed in one cat after the injection of GABA 1 mg and in three cats after the injection of GABA 2–5 mg, given in divided doses of 1 mg at 15 min intervals. Complete respiratory paralysis lasting for more than 1 hr was observed in all cats when the dose required for transient respiratory paralysis was doubled.

Circulatory and respiratory effects of intracisternal GABA usually developed after a latent period of one up to several minutes. In two cats, in which 0·01 and 0·1 mg intracisternal GABA produced a transient rise of the blood pressure, GABA 10 mg/kg I.V. produced hypotension.

Experiments on the isolated perfused rabbit, rat and guinea-pig heart. Hearts from three rats and two guinea-pigs were used and no effect was obtained when up to GABA 10 mg was added to the perfusion fluid. In the rabbit heart (2 experiments) GABA 0·1 mg and higher doses slightly enhanced the force of contractions but had no effect on the rate. The maximum effect represented a 15% increase in the force of contractions. These findings show that mammalian and crustacean hearts respond differently, since GABA slows force and rate of contractions in the latter (Enger & Burgen, 1957; Brockman & Burson, 1957). GABA 10 mg had no effect on the response of the isolated rabbit heart to acetylcholine or adrenaline when the latter were given 30 sec after GABA.

Experiments on perfused hind limbs. In both rats and guinea-pigs GABA 1 mg occasionally produced a just noticeable transient increase in flow. GABA 10 mg consistently increased the flow by up to 25%. This effect was abrupt in onset and lasted for not longer than 1 min.

GABA–strychnine antagonism in mice. To investigate the effectiveness of peripherally administered GABA as an antagonist of a central stimulant, experiments were carried out on mice. Intraperitoneal GABA 0·2 ml. was given and 5 min later strychnine nitrate 0·2 ml. was injected subcutaneously. With all doses of strychnine the mice injected with GABA 0·5 mg per mouse showed a mortality similar to that observed in the control group. When GABA 5 or 50 mg per mouse was given and strychnine was used in a dose which produced partial mortality in the control group, female mice appeared to be

protected in 2 out of 3 experiments but the opposite result was obtained in a fourth experiment. In male mice the difference between the number of survivors in GABA-treated and control groups was always negligible. No protection was obtained in either male or female mice if strychnine was given in doses which were 1·5–2 times greater than those which produced an approx. 75% mortality in control groups. These results are presented in Table 1.

TABLE 1

Sex	Strain	Weight (g)	Dose of strychnine nitrate (μg/mouse)	Number of animals killed / Number of animals injected		
				No pre-treatment	GABA 5 mg	GABA 50 mg
♀	MVH	19–21	10	0/4		
			20	3/4 (9)	0/6	
			40	2/2 (6)	2/2 (4)	2/2 (8)
♀	CF_1	18–20	15	0/2		
			20	5/7 (8)	3/7 (14)	1/3 (21)
			30	3/3 (7)	3/4 (11)	4/4 (17)
♀	CF_1	17–18	20	5/4 (10)		10/14 (18)
♀	CF_1	18–20	20	1/3 (19)		
			30	5/6 (14)	0/3	0/3
♂	MVH	24–27	10	0/2		
			20	2/3 (14)	2/4 (7)	
♂	CF_1	21–24	25	1/4 (20)	1/4 (18)	
			30	3/4 (16)	3/4 (19)	1/4 (21)
♂	CF_1	12–14	10	1/4 (16)		
			12·5	2/4 (5)		3/4 (17)
			15	7/8 (7)	3/4 (18)	6/8 (23)

The effect of GABA on the toxicity of strychnine in mice. The toxicity of strychnine was judged by its lethal effect. Each mouse in the control group, listed under the heading 'no pretreatment', received saline 0·2 ml. intraperitoneally, and 5 min later strychnine 0·2 ml. subcutaneously. Mice receiving GABA were given an injection of GABA 0·2 ml. intraperitoneally, instead of saline, and each mouse received the quantity of GABA indicated in the heading. The figures in brackets are the mean survival times in minutes for each group.

DISCUSSION

GABA I.V. has both circulatory and respiratory actions in rabbits, dogs and cats anaesthetized with urethane, sodium thiopentone and chloralose, respectively. In the first two species and in most cats the circulatory effects of GABA consist mainly in a transient lowering of the blood pressure. Graded falls of the blood pressure are achieved over a 10–100 fold range of doses and the duration of hypotension is determined by the dose. Higher doses of GABA produce complete desensitization to GABA and the duration of desensitization is proportional to the desensitizing dose.

Slowing of the heart by GABA is negligible in rabbits and cats but in dogs marked bradycardia follows the injection of GABA 0·1 mg/kg or higher doses.

Respiratory effects of GABA vary between species. In rabbits, and to a much smaller extent in cats, varying degrees of respiratory stimulation are

seen, but in dogs GABA consistently depresses the respiration. All respiratory effects are transient, rapid in onset and either coincide with the fall of the blood pressure or precede the latter by a few seconds.

A comparison of circulatory and respiratory effects of intravenous and intracisternal GABA shows that in dogs the effects of intravenous GABA are not the result of a direct action of GABA on the brain stem. In cats the possibility that in some experiments a part of the effect of intravenous GABA is attributable to an action of GABA on the brain stem cannot be excluded with certainty, on the basis of the experimental evidence presented. Purpura *et al.* (1958) have shown that in cats GABA does not penetrate the blood-brain barrier in effective concentrations. van Gelder & Elliott (1958) showed that the concentration of GABA in the cerebrospinal fluid of cats anaesthetized with chloralose was 1·4–3·3% of that in the blood after the intravenous injection of large doses of GABA. Relatively high concentrations of GABA are required to produce effects on the cat's cerebral cortex (Iwama & Jasper, 1957). Thus it seems unlikely that in cats a central action of GABA could account for the major part of the circulatory effects of intravenous GABA.

Attempts to elucidate the mechanism by which the circulatory effects of intravenous GABA are accomplished provided the following information. In rabbits neither atropine nor bilateral vagotomy modifies the circulatory action of GABA, but ganglion block reduces it slightly. Experiments on perfused rabbit hearts show that GABA does not lower the blood pressure by reducing the force of ventricular contractions. GABA also has no effect on the response of the isolated rabbit heart to acetylcholine or adrenaline. In dogs some of the bradycardia produced by GABA is dependent on the intactness of the vagus, but bilateral vagotomy only slows the onset of hypotension without affecting it otherwise and the hypotensive response in vagotomized dogs is atropine-resistant. In cats under sodium pentobarbitone anaesthesia GABA 100 mg/kg fails to modify chemo- and baroreceptor activity in the sinus nerve (unpublished observations). Since previous work (Hobbiger, 1958*a*, *b*) has shown that some peripheral actions of GABA are markedly species-dependent it is not advisable to use information obtained in one species for the interpretation of results obtained in another species. The finding that GABA 1–10 mg produces a transient vasodilatation in perfused hind limbs of rats and guinea-pigs might thus be of little significance for other species.

One possible way in which GABA could produce hypotension is by affecting the vasoconstrictor tone of blood vessels. Since the circulatory actions of GABA in rabbits are only slightly reduced by pentamethonium, reduction in the activity of the sympathetic nervous system is certainly not the main cause of the GABA-induced hypotension in this species. The marked ganglion-blocking action which Florey & McLennan (1955) observed with Factor I, a crude preparation of GABA obtained from mammalian brain, on the isolated

inferior mesenteric ganglion of the rabbit, does not necessarily contradict our interpretation of results, since McLennan (1957) has shown that GABA and Factor I differ considerably in their actions. In the cat reduction in the activity of the sympathetic nervous system also seems to contribute little if anything to the circulatory action of GABA, since only a slight reduction in the effectiveness of preganglionic stimulation of the nictitating membrane by submaximal stimuli was observed after the I.V. injection of GABA 10–100 mg/kg (unpublished observations). The possibility that GABA acts by releasing a vasodilator material appears unlikely since the fall of the blood pressure occurs abruptly in all species and the delay between injection of GABA and onset of action is short.

The question arises as to what extent the work in animals under anaesthesia provides useful information for the interpretation of the action of intravenous GABA in the conscious man. The following experiments seem to throw some light on this. Comparable results were obtained in rabbits anaesthetized with urethane, chloralose or sodium thiopentone, and Takahashi *et al.* (1955) have reported that in unanaesthetized rabbits the effects of GABA were qualitatively the same but shorter-lasting than in rabbits under urethane anaesthesia. The tracings published by Takahashi *et al.* (1955) show, however, that in conscious rabbits GABA has a marked respiratory stimulant action which is not preceded by a phase of depression. In cats hypotensive responses were obtained when either chloralose or sodium pentobarbitone were used as anaesthetic agents but in unanaesthetized cats and in some cats under chloralose anaesthesia GABA had a hypertensive action. The action of GABA in the conscious man resembles more closely the action of GABA in the dog under sodium thiopentone anaesthesia than that in other species. However, whereas in man GABA produces the sequence tachybradia → bradycardia → tachycardia, in the anaesthetized dog GABA produces only bradycardia. Since in many experiments carried out under anaesthesia a very transient and just detectable rise of blood pressure preceded the hypotension, it is possible that anaesthesia masks some stimulant actions of GABA, and experiments in unanaesthetized dogs might reproduce the effects of GABA in man even more closely than experiments in dogs under sodium thiopentone anaesthesia.

The outcome of the experiments on the effect of GABA on strychnine poisoning in mice was not unexpected. As has been pointed out previously, GABA does not pass the blood-brain barrier easily, and recent experiments of Jasper, Gonzalez & Elliott (1958) have shown that GABA and strychnine are not antagonistic as far as their action on the action potentials of the mammalian cortex is concerned. In our experiments, GABA 50 mg/per mouse failed to protect mice against the lethal action of strychnine if strychnine was given in 1·5 times the dose which produced a mortality not exceeding

75%. When strychnine was used in doses which produced only partial mortality in the control group, apparent protection was observed on two occasions in female but never in male mice. However, if all the experimental results are combined no significant GABA–strychnine antagonism could be demonstrated. Since vascular actions of the high doses of GABA used cannot be excluded as a factor responsible for minor changes in strychnine toxicity it seems to us that there is at present no evidence for an antagonism of strychnine and GABA resulting from an action of the two substances on the central nervous system. The observations with higher doses of strychnine agree with the findings of Brockman & Burson (1957).

SUMMARY

1. The circulatory actions of γ-aminobutyric acid (GABA) I.V. were studied in rabbits, dogs and cats under urethane, sodium thiopentone and chloralose anaesthesia, respectively. In the first two species and in most cats GABA lowered the blood pressure. This effect was quick in onset, transient and repeatable when smaller doses of GABA were given at suitable intervals. Higher doses of GABA produced desensitization.

2. In dogs the fall of the blood pressure was associated with marked bradycardia, which was less marked if GABA was injected after bilateral vagotomy.

3. The action of GABA on the blood pressure of rabbits and of vagotomized dogs is atropine-resistant, and on isolated rabbit hearts GABA does not depress the myocardium.

4. Experiments in which GABA was given intracisternally indicate that the circulatory effects of GABA I.V. in dogs and most probably in cats are not due to an action on the brain stem.

5. The hypotensive action of GABA was also observed in rabbits anaesthetized with chloralose or sodium thiopentone and in cats anaesthetized with sodium pentobarbitone, but a transient rise of the blood pressure was obtained in some cats under chloralose anaesthesia and in unanaesthetized cats.

6. In conscious man GABA 50–100 mg I.V. produced transient hypotension, and bradycardia preceded and followed by tachycardia.

7. The respiratory effects of intravenous GABA in anaesthetized animals were abrupt in onset, transient and species-dependent. In rabbits, and to a much smaller extent in cats, GABA stimulated the respiration but in dogs it consistently depressed it.

8. No antagonism by GABA against lethal doses of strychnine could be demonstrated in mice.

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