

## CAROTID CHEMORECEPTOR REFLEX IN RATS DURING EXPERIMENTAL TETANUS TOXICITY

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**Abstract**—1. The effects of stimulation of carotid body chemoreceptors on blood pressure, heart rate and ventilation were compared in normal rats and rats with local or generalised tetanus toxicity induced by injection of the toxin.

2. Carotid chemoreceptor stimulation resulted in an increase in blood pressure and a decrease in heart rate in both control and tetanus rats.

3. However, while chemoreceptor stimulation resulted in increases in ventilation of 115% and 123% in normal rats and rats with local tetanus respectively, the increase in rats with generalised tetanus was only 29%.

4. The experiments indicate that normal rats and rats with tetanus toxicity exhibit identical pressor and heart rate responses to stimulation of carotid chemoreceptors whereas the ventilatory response is attenuated in the tetanus rats.

### INTRODUCTION

Tetanus toxicity has been associated with derangements of various functions in the body, particularly the central nervous, cardiovascular and respiratory systems. There is increased excitability of the motoneurone resulting in muscle rigidity (Brooks *et al.*, 1957). The respiratory changes are attributable to rigidity and spasms of the respiratory muscles resulting in hypoventilation and various degrees of hypoxaemia (Femi-Pearse, 1974). Cardiovascular manifestations due mainly to an increase in sympathetic nervous activity result in increases in blood pressure, heart rate and cardiac contractility (Kerr *et al.*, 1968; Odusote and Sofola, 1976; Alfred and James, 1974).

Carotid chemoreceptor reflexes have been shown to result in attenuated pressor responses when systemic blood pressure is elevated (Heistad *et al.*, 1974), in spontaneously hypertensive rats (Sofola and Egbe, 1981), or when carotid sinus pressure is increased (Hainsworth *et al.*, 1978). Since tetanus results in a high sympathetic tone and a consequent increase in basal blood pressure, we have decided to find out the effect of carotid chemoreceptor stimulation if any, during induced tetanus in rats. In addition, the ventilatory responses were also examined in order to find out if these responses are also affected.

### MATERIALS AND METHODS

Experiments were carried out on albino Wistar rats of either sex, weighing between 220 and 300 g. The rats were divided into three experimental groups as follows: (a) control rats (b) rats with generalised tetanus (c) rats with local tetanus. Tetanus was induced by s.c. injection of tetanus toxin (Swiss Serum and Vaccine Institute, Berne) into a thigh, at a dose of 3000 MLD/kg. The rats developed local tetanus, as evidenced by extension of the injected limbs,

usually after 18 hr. This then progressed to generalised tetanus, characterised by spasms, which occurred about 24–30 hr after toxin injection. Control rats had sterile saline injected into the thigh.

The rats were anaesthetized by i.p. injection of urethane (BDH Chemicals Ltd, Poole) at a dose of 1.5 g/kg body weight. After induction of anaesthesia, a mid-line incision was made in the neck in order to isolate the trachea and the common carotid arteries. The trachea was cannulated by means of a polyethylene cannula with an internal diameter similar to that of the trachea. The tracheal cannula was then connected to a Fleisch Pneumotachograph and then to a Grass Integrator via a volumetric transducer (model PT 5A) to a Grass Polygraph (model 7D, Grass Instruments, Quincy, Mass) for the recording of tidal volume. The pneumotachograph was calibrated using a 5 cm<sup>3</sup> syringe. Respiratory frequency was computed from the number of tidal volume in 15 sec and converted to rate per minute. Minute ventilation ( $V_E$ ) was calculated from the product of tidal volume and respiratory frequency.

One common carotid artery was ligated and then cannulated both ways; peripherally for the recording of arterial blood pressure and cranially for the injection of drugs to stimulate the carotid body chemoreceptors. The pressure cannula was connected via a statham pressure transducer to the Grass Polygraph and the transducer was calibrated using a mercury manometer. Mean blood pressure was calculated from the sum of the diastolic pressure and one-third pulse pressure. Heart rate was computed from the number of arterial pulses per minute.

The carotid chemoreceptors were stimulated by the intracarotid injection of either 20 µg of nicotine or 0.2 ml of 0.5 M solution of sodium dithionide (Henderson and Ungar, 1978; Sofola and Egbe, 1981). The sodium dithionide was freshly prepared on each experimental day and stored under liquid paraffin. The injected volume which was 0.2 ml in each case was warmed to 39°C in a thermostatically controlled water bath (Grants Instruments Ltd, Cambridge, England) and administered slowly over a period of 5 sec.

Experiments were performed on 10 control rats, 9 rats with generalised tetanus toxicity and 4 rats with local tetanus. Control records of arterial blood pressure (BP), heart rate (HR), tidal volume (TV) and respiratory frequency (F) were taken. Then the chemoreceptor stimulant, either nicotine or sodium dithionide, was administered. The

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Table 1. Blood pressure and heart rate responses to carotid chemoreceptor stimulation in control rats and rats with tetanus

	Blood pressure (mmHg)		Heart rate (beats/min)	
	C	T	C	T
Normal rats ( <i>n</i> = 10)	133 ± 6	155 ± 8 ( <i>P</i> 0.001)	380 ± 17	338 ± 14 <i>P</i> = NS
Generalised tetanus rats ( <i>n</i> = 9)	147 ± 3	178 ± 6 ( <i>P</i> 0.001)	409 ± 10	369 ± 16 <i>P</i> = NS
Rats with local tetanus ( <i>n</i> = 4)	151 ± 4	165 ± 5 ( <i>P</i> 0.025)	390 ± 14	339 ± 25 <i>P</i> = NS

C = Control; T = Test period; *n* = Number of rats.

changes in the measured variables were then determined. The responses were compared in normal control rats, rats with generalised tetanus and rats with local tetanus. The magnitude of the responses were analysed in each group of rats and also between the tetanus rats and the control rats. In addition, the effects of i.v. injection of 2 mg/kg of diazepam on the responses if any, were also tested. Statistical analyses of the data were compared in each group of rats using the paired *t*-test and between groups of rats using the Student's *t*-test.

## RESULTS

### Blood pressure and heart rate responses

In the control rats, the mean basal blood pressure (BP) was 133 ± 6 mmHg while in the tetanus rats, the basal BP was 147 ± 3 mmHg for rats with generalised tetanus and 151 ± 4 mmHg for those with local tetanus. The basal heart rates (HR) were 380 ± 17 beats/min in control rats, 409 ± 10 beats/min in rats with generalised tetanus and 390 ± 14 beats/min in rats with local tetanus.

Following carotid chemoreceptor stimulation, BP increased in all the groups of rats: from 133 ± 6 to 155 ± 6 mmHg (17%) in control rats, 147 ± 3 to 178 ± 5 mmHg (22%) in rats with generalised tetanus

Table 2. Ventilatory responses to carotid chemoreceptor stimulation in rats (ventilation—ml/min)

	Normal rats	Generalised tetanus rats	Local tetanus rats
Control	472 ± 33	738 ± 62	562 ± 66
Test	1013 ± 71	953 ± 108	1255 ± 123
Per cent change	115%	29%	123%
<i>n</i> =	10	9	4
<i>t</i> -paired	7.2432	3.7288	4.0174
<i>P</i> =	0.001	0.01	0.05

and from 151 ± 4 to 165 ± 5 mmHg (10%) in rats with local tetanus. All the increases in each group were statistically significant (*P* = 0.001, 0.001 and 0.025 respectively). On the other hand, heart rate was decreased from 380 ± 17 to 338 ± 14 beats/min (11%) in control rats, 409 ± 11 to 369 ± 16 beats/min (10%) in rats with generalised tetanus and from 390 ± 14 to 338 ± 25 beats/min (13%) in rats with local tetanus. These decreases however were not statistically significant. These changes are all summarized in Table 1.

### Ventilatory responses

In the normal rats, minute ventilation ( $V_E$ ) in ml/min, increased from 472 ± 33 to 1013 ± 71 (115%) after chemoreceptor stimulation, while in the rats with local tetanus it increased from 562 ± 66 to 1255 ± 123 (123%). However, in the rats with generalised tetanus, the increase was only 29%, from 738 ± 62 to 953 ± 108. In all the three groups, these increases were statistically significant. However, the increase in ventilation in the rats with generalised tetanus is statistically less (*P* = 0.05) when compared with that in the other groups. An example of such a response is shown in Fig. 1 and Table 2 summarises the ventilatory responses in the three groups.

### Effect of diazepam

The effect on the response of i.v. injection of diazepam at a dose of 2 mg/kg body weight was also

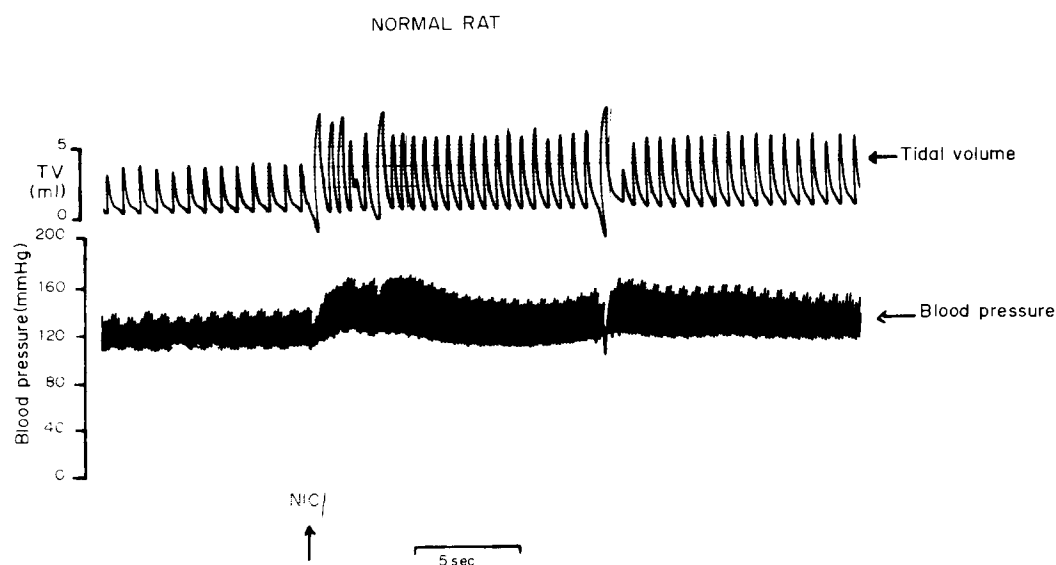


Fig. 1. Pressor and ventilatory response to intracarotid injection of nicotine in a control rat.

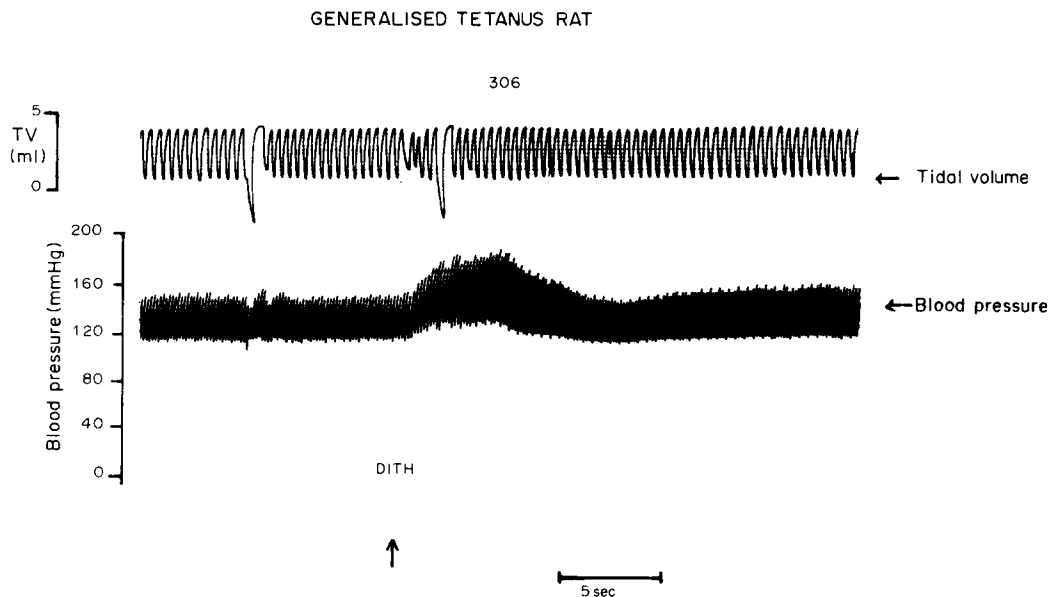


Fig. 2. Intracarotid injection of dithionite in a rat with generalised tetanus. Note pressor response despite the lack of ventilatory response.

tested. However, in all groups of rats, the ventilatory response was markedly attenuated. In the control group, the ventilatory response to chemoreceptor stimulation was only 32% compared to an increase of 115% without diazepam. However, in rats with generalised tetanus who demonstrated a blunted ventilation response to chemoreceptor stimulation (29%), the administration of diazepam resulted in a further small reduction in response (20%).

#### DISCUSSION

It has previously been established that normotensive rats exhibit pressor and ventilatory responses to stimulation of carotid chemoreceptors (Sofola and Egbe, 1981). On the other hand, in spontaneously hypertensive rats of the Aoki-Okimoto strain (Sofola and Egbe, 1981), a high arterial blood pressure induced by elevation of systemic pressure (Heistad *et al.*, 1974) or a high carotid sinus pressure (Mancia, 1978; Hainsworth *et al.*, 1978) all appear to attenuate the pressor response to carotid chemoreceptor stimulation. This phenomenon has been explained in terms of interaction between baroreceptors and chemoreceptors at the central nervous system level resulting in inhibition of chemoreceptor reflexes by the baroreceptors (Mancia, 1975).

In rats developing tetanus, high basal values of blood pressure have been described earlier (Sofola, 1982) and are also seen in the present experiments. However, in these tetanus rats, carotid chemoreceptor stimulation still gave comparable increases in blood pressure as in control rats without tetanus. This indicates that the high sympathetic tone seen during tetanus in many species (Odusote and Sofola, 1976; Sofola, 1982) does not appear to influence

chemoreceptor responses during tetanus. Similarly, baroreceptor reflexes appear to be uninfluenced during experimental tetanus in dogs (Odusote and Sofola, 1976).

The ventilatory changes observed during the present experiments demonstrate striking dissimilarities in the magnitude of response by rats with generalised tetanus when compared with control rats. In response to carotid chemoreceptor stimulation, the rats with generalised tetanus toxicity exhibit an attenuated ventilatory response when compared to control rats or rats with local tetanus. The increase in ventilation in the rats with generalised tetanus was statistically less than that in other groups of rats. The explanation for this may be due to the fact that the rats with generalised tetanus do have muscle rigidity and spasms as part of the picture in tetanus (Elegbeleye, 1978) so that despite any ventilatory drive, the respiratory muscles are not able to respond adequately.

The implication of this finding is that tetanus patients with muscle rigidity and consequent hypoxaemia, which has been reported (Femi-Pearse, 1974; Elegbeleye, 1978) may experience chemoreceptor drive which they may not be able to respond to. This factor may have implications in terms of aggravating the hypoxaemia since they cannot hyperventilate in order to minimize the hypoxaemia which may result in increased morbidity in such patients. Diazepam does not appear to be of much help in such circumstances, because being a muscle relaxant, the muscles would not respond adequately to any ventilatory drive.

In conclusion, it has been shown that rats developing tetanus exhibit identical pressor response to carotid chemoreceptor stimulation as in normal rats whereas the ventilatory response is attenuated in rats with generalised tetanus.

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