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Title : BRAIN SEROTONIN AND THE RESPONSE TO HEMORRHAGE

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**Introduction.** Brain serotonin containing neurons have been proposed to modulate respiratory drive<sup>1</sup> and sympathetic response to stress<sup>2</sup>. Since both respiratory activity and sympathetic responses are dramatically altered in response to hemorrhage, we examined if rats with a decrease in numbers of CNS serotonin containing nerve terminals evidence any alteration in their response to hemorrhage. Our results suggest that sequential hemorrhage more severely reduces blood pressure in rats which have lost 70-80% of their serotonergic neurons. However, the depletion of cerebral cortical ATP content by an equal amount of hypoxia-hemorrhagic hypotensive stress was unaltered by the neuronal loss. These results suggest that in the awake rat the circulatory response to hemorrhage is modulated by CNS serotonergic neurons, but shock-induced changes in cortical ATP content are not dependent on or antagonized by serotonergic innervation.

**Methods.** Unfasted 400-600g rats were lightly anesthetized with ether and the ventral tail artery was cannulated to permit blood gas analysis and monitoring of blood pressure (BP) and heart rate (HR). The animals were allowed to recover for 20 min in a circular chamber which permitted unrestricted movement, and were given 100% O<sub>2</sub> to breath. After recording baseline HR, BP, PaO<sub>2</sub>, PaCO<sub>2</sub> and pH, the rats were bled of 0.7% of their body weight in grams. This hemorrhage was repeated 3 additional times at 10 min intervals, with HR and BP recorded at 5 and 10 min intervals, and blood gases at 10 min after each hemorrhage. These experiments were performed in rats given 50mg/kg i.p. pargyline at 3 days of age (Control) or pargyline and 50µg 5,7-dihydroxytryptamine (5,7-DHT) intracisternally.

In order to assess metabolic effects of hypoxic-hypotension, rats were anesthetized with sodium pentobarbital (50mg/kg i.p.), and ventilated through a tracheostomy with 30% O<sub>2</sub>-70% N<sub>2</sub>O to produce a PaCO<sub>2</sub> of 35-40. After baseline measurements, hypoxic (FIO<sub>2</sub> = 0.075) hemorrhagic (mean arterial pressure = 30 mm Hg) hypotension was produced for 30 min by removing blood through a femoral artery cannula. Animals not used to establish baseline or shock values were killed either 20 min (S+20) or 120 min (S+120) after reinfusion of shed blood. These experiments were conducted in animals given pargyline 50mg/kg i.p. 10-14d previously (Control) or intracisternal 5,7-DHT (50µg) 30 min after pargyline as above. The brain of each rat was quickly frozen *in situ* by pouring liquid nitrogen into a chimney placed on the exposed skull.<sup>3</sup> CNS serotonin, dopamine, and norepinephrine were measured as described previously.<sup>1</sup> Brain lactate, ATP, and ADP were measured using the techniques of Lowry and Passonneau<sup>4</sup>.

### Results.

#### Cardiovascular Responses to Progressive Hemorrhage

Group	Post Hemorrhage #3					
	Equilibrium		5 min		10 min	
	BP	HR	BP	HR	BP	HR
Control	110±3	382±7	68±14	333±28	70±14	317±29
5,7-DHT	103±5	367±15	24±2	175±35	46±15	218±30

The cardiovascular responses were not significantly different after the first two hemorrhages, but after the third the 5,7-DHT treated rats responded with a greater decrease in blood pressure and heart rate (p<.01). The changes in blood gas and rectal temperature were similar in both groups.

#### Effects of Hemorrhage on Cerebral ATP and Serotonin Content

		Baseline	Shock	S+20	S+120
		Control	ATP 2.75±.06	2.04±0.12	2.36±.07
	5HT	251±21	457±114	304±55	294±37
	M	7	8	9	8
5,7-DHT	ATP	2.67±.04	1.62±.35	2.21±.10	
	5HT	72*	199±21	52±19*	
	M	2	5	8	

Control rat brain ATP is sharply reduced (p<.01) by the shock treatment, and a simultaneous increase (p<.05) in serotonin is noted acutely, but decreases rapidly toward control values with recovery from shock. The values of ATP produced by shock in 5,7-DHT treated rats are not significantly lower than in control rats at corresponding time intervals, and the serotonin content still increases, though from a lower baseline during shock, and decreases again with recovery from shock.

**Discussion.** Our data would suggest that CNS serotonin containing neurons do not participate in the respiratory response to hemorrhage, nor do they determine the degree of change in cerebral cortical ATP which occurs with hypoxic hypotensive shock. It is also unlikely that the changes in cerebral perfusion, edema and blood brain barrier integrity which follow the shock state are a simple function of changes in serotonin content since these values quickly decrease towards control values after termination of the shock state. Changes in serotonin release could still be involved, however, since content of amine does not reflect utilization. The greater sensitivity of the 5,7-DHT treated rat to hemorrhage suggests that as in hypertension, serotonin may modulate the sympathetic response to hemorrhage.

#### References.

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