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Cardiovascular Functions of Central Noradrenergic and Serotonergic Neurons in Conscious Rabbits

Their Contributions to the Central Actions of Clonidine

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Synaptic release of transmitter from central noradrenergic (NA) and serotoninergic (5HT) neurons was studied in intact and pontine decerebrate unanesthetized rabbits, following intracisternal injections of the selective neurotoxic drugs 6-hydroxydopamine (6-OHDA) and 5,6-dihydroxytryptamine (5,6-DHT). The NA and 5HT neurons both raise blood pressure through a suprapontine pathway, with 5HT neurons in series with NA neurons. Descending bulbochial fibers have antagonistic effects on blood pressure, with NA release lowering blood pressure and 5HT release increasing it. The two transmitters also have antagonistic effects on the cardiac vagus, with NA neurons increasing vagal activity and 5HT neurons inhibiting it. Our results suggest that both NA and 5HT neurons contribute to the cardiovascular effects of clonidine. The actions of clonidine on blood pressure and heart rate mimic the effects of NA and are opposite those of 5HT released at synaptic sites in the bulb and spinal cord.

Many of the cardiovascular effects of clonidine occur through stimulation of α-adrenoceptors in the CNS. We compared the actions of clonidine on blood pressure and heart rate with the effects of stimulation of central noradrenergic (NA) and serotoninergic (5HT) neurons, since both contribute to the cardiovascular actions of clonidine.1 Each of the above groups of neurons have their cell bodies in several distinctive nuclei in the pons and medulla.4 From

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some cells axons ascend to several supratentorial sites, while from others axons project to other bulbar nuclei, to the cerebellum, and to the preganglionic sympathetic motoneurons of the spinal cord. There has been much controversy about the functions of NA and 5HT neurons, which is at least partly due to the considerable differences in methods used to study them. We based the analysis of the functions of these neurons on the cardiovascular effects produced during the phase of transmitter release during the first few hours after injecting the selective neurotoxic drugs 6-hydroxydopamine (6-OHDA) and 5,6-dihydroxytryptamine (5,6-DHT). When given in appropriate doses, each drug is selectively taken up at the specific neuron terminal by an active transport mechanism. This is followed successively by transmitter release, neuronal block, and eventual destruction of the nerve terminal. The phase of transmitter release lasts for several hours and is associated with large cardiovascular effects. To separate the effects of transmitter release at supratentorial sites from those occurring in bulbar or spinal brain regions, we studied the acute effects of intracisternal (IC) injections of 6-OHDA and 5,6-DHT neurotoxins in unanesthetized rabbits and in pontine decerebrate preparations.

Functions of NA Neurons

In intact rabbits IC 6-OHDA (600 μg/kg), given by indwelling IC catheter produced a rise in mean arterial pressure (MAP) and bradycardia (Fig 1). The rise in MAP began after about one hour and was often preceded by a small fall in blood pressure. The peak pressor response and bradycardia usually occurred between two and three hours after injection. Pretreatment with IC phentolamine (200 and 500 μg/kg) prevented the bradycardia and produced dose-related attenuation of the pressor response.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21340/)

**Figure 1.** Average changes in mean arterial pressure (Δ MAP; mm Hg) and heart rate (Δ HR; b/min) following intracisternal (IC) injection of the neurotoxic drugs 6-OHDA or 5,6-DHT (solid lines) or appropriate vehicle (interrupted lines) in unanesthetized rabbits. *Two left panels*, intact rabbits; *two right panels*, pontine decerebrate preparation. (From Korner PI, Head GA, with permission.)

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21340/)

**Figure 2.** Time course of changes in mean arterial pressure (Δ MAP) and heart rate (Δ HR) after 1 μg/kg IC clonidine (arrow) in different groups of rabbits. *Left*, average responses of six rabbits obtained before (control, open circles) and seven days after injection of ascorbic acid vehicle (vehicle, closed circles). *Middle*, average responses in ten rabbits before (control, open circles) and seven days after 6-OHDA (600 μg/kg IC) (6-OHDA, closed squares). *Right*, results in five rabbits seven days after 5,6-DHT (633 μg/kg IC) (5,6-DHT, closed triangles) and after injecting creatine sulfate vehicle (vehicle, closed circles). (From Korner et al., by permission.)
Mitter-stimulating central $\alpha$-adrenoceptors. At the large doses used, phentolamine probably blocked effects mediated through both $\alpha_1$- and $\alpha_2$-adrenoceptors.

In pontine rabbits given the same dose of IC 6-OHDA, there was a fall in MAP and, again, significant bradycardia (Fig 1). The time course of these changes was similar to the effects of IC clonidine on the above variables 8 (Fig 2).

We also studied the effects of IC 6-OHDA on the properties of the baroreceptor-heart rate reflex which were characterized by sigmoid MAP-heart period (HP) function curves. 8 In normal rabbits, following injections of 6-OHDA, the HP range between upper and lower plateaus of the curve increased significantly from control, as did the average gain (slope) (Fig 3). Similar changes in these parameters were also observed in pontine rabbits. The rise in HP range was entirely due to elevation of the upper curve plateau, suggesting that release of transmitter altered heart rate by facilitating cardiac vagal efferent activity. The only differences between intact and pontine preparations were in the median blood pressure (BP50) (and in the threshold for eliciting bradycardia), which increased above control in intact rabbits and decreased in pontine animals. 8 The changes in threshold and BP50 can be accounted for entirely by rapid resetting of the arterial baroreceptors themselves 5,9 by the different changes in resting MAP occurring in the two preparations after 6-OHDA (Fig 1).

In summary, release of transmitter at bulbar or spinal NA neurons lowers blood pressure and reduces heart rate, mainly through vagal efferent facilitation. On the other hand, release of transmitter at suprapontine NA terminals produces a rise in MAP, which is due to systemic vasoconstriction of mainly the renal and splanchnic vascular beds. 8

**FUNCTIONS OF 5HT NEURONS**

The acute circulatory effects in intact rabbits following IC administration of 5,6-DHT (633 $\mu$g/kg) consisted of a biphasic pressor response and a rise in heart rate (Fig 1). The initial rise in MAP was transient, while the second component was well sustained. 8 Injection of creatinine sulfate vehicle also produced an early, transient rise in MAP which was significantly smaller than the early pressor component after 5,6-DHT. 8 Pretreatment with IC methysergide attenuated or abolished the heart rate changes and the late component of the pressor response, suggesting that they were due to 5HT release. 8

In pontine rabbits IC 5,6-DHT again produced an early, transient rise in MAP, but the late component was no longer present (Fig 1). There was now no change in blood pressure after creatinine sulfate vehicle, so that the difference between the responses after the neurotoxic drug and vehicle was about the same as in intact rabbits. In pontine rabbits 5,6-DHT again resulted in tachycardia, which was of about the same magnitude as in intact rabbits (Fig 1). 8

The acute effects of 5,6-DHT on the baroreceptor-heart rate reflex consisted of a reduction in HP range and in gain (Fig 3). The fall in HP range was entirely at the expense of the upper HP plateau, signifying that 5HT release inhibited vagal efferent activity. This also accounted for the increase in resting heart rate after 5,6-DHT.

Thus, after 5,6-DHT, synaptic release of 5HT elevates MAP through a suprapontine pathway and raises heart rate by vagal inhibition through a bulbar pathway. The evidence that the early component of the pressor response is also due to 5HT release at bulbar or spinal 5HT terminals is somewhat less compelling, since it was not abolished by methysergide. 8 Nevertheless, this component was probably also caused by 5HT release, in view of the findings of de Groat and Ryall, 13 that neural discharge increased after direct iontophoretic application of 5HT to preganglionic sympathetic motor-neurons.
INTERRELATIONSHIP BETWEEN NA AND 5HT NEURONS

The suprapontine 5HT pressor pathway is in series with the NA pressor pathway (Fig 4). This was demonstrated in experiments in which the acute effects of 6-OHDA (or 5,6-DHT) were studied after previous destruction of 5HT (or NA) neurons by IC administration of the other neurotransmitter one week previously. The characteristic rise in MAP produced by 6-OHDA was not altered by previous administration of 5,6-DHT, but the late component of the pressor response was abolished by previous destruction of NA neurons.

By contrast, the characteristic heart rate changes and alterations in baroreflex properties produced by each neurotransmitter were not affected by prior administration of the other drug. This is illustrated schematically in Figure 4, which shows that bulbar NA heart rate neurons facilitate cardiac vagal efferent activity, while 5HT neurons have the opposite effect through a parallel pathway. Descending reticulospinal NA and 5HT pathways exert similar antagonistic control on spinal preganglionic sympathetic neurons, which are inhibited by descending NA fibers and excited by 5HT fibers.

NA AND 5HT NEURONS AND THE ACTIONS OF CLONIDINE

We studied the effect on blood pressure and heart rate of 1 μg/kg IC clonidine, which is a near maximal dose.1 In one group of rabbits clonidine produced closely similar effects on two occasions, seven days apart, before and after administration of ascorbic acid vehicle (Fig 2, left). In another group of rabbits clonidine was administered before and seven days after giving 6-OHDA, which reduced spinal and bulbar catecholamines to 20 percent and 60 percent of control, respectively.2 After destruction of the NA neurons, the maximum fall in MAP produced by clonidine was virtually the same as before 6-OHDA, although the onset was somewhat slower (Fig 2, middle). However, the early component of the bradycardia was abolished, and the late component was considerably attenuated (Fig 2, middle).3 We also studied a third group of rabbits seven days after IC administration of 5,6-DHT; another group was studied after injecting creatinine sulfate vehicle. After 5,6-DHT, the falls in blood pressure and heart rate were both significantly smaller and of slower onset than in vehicle-injected rabbits (Fig 2, right).4

These results suggest that both NA and 5HT neurons contribute to the vagal component of normal bradycardia response to IC clonidine. Clonidine mimics the bulbar effects of synaptic NA release on heart rate; from the effects observed after destruction of 5HT neurons, it seems probable that clonidine may contribute to the bradycardia by inhibiting 5HT neurons controlling vagal tone. Since clonidine not only excites the vagus but also inhibits the cardiac sympathetic,1,5 it is possible that transmitters other than NA and 5HT may contribute to the heart rate changes after the drug. The effects of clonidine on MAP are similar to those of synaptic release of NA through the descending bulbospinal pathway and are opposite the effects of 5HT release, suggesting that clonidine stimulates NA neurons and inhibits 5HT neurons controlling blood pressure.

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