Neurogenic Regulation of Coronary Blood Flow: Evidence for a Central Nervous System Pathway


The central representation of neurogenically mediated coronary vasoconstriction produced by activation of the sympathetic nervous system was examined in anesthetized cats instrumented for continuous recording of coronary and femoral blood flows, arterial pressure, and heart rate. Electrical stimulation in a small region of perifornical lateral hypothalamus increased arterial pressure, heart rate, and coronary blood flow; following the administration of propranolol, a transient coronary vasoconstrictor response was unmasked. The response was mediated over the sympathetic nervous system since it was blocked by stellate ganglionectomy and by the alpha-adrenergic receptor antagonist prazosin. Projections to and from the lateral hypothalamic site were identified by using anterograde and retrograde pathway-tracing techniques. Paraventricular nucleus projected to lateral hypothalamus, which in turn made connections in periaqueductal gray with projections terminating in lateral reticular formation of medulla. Coronary vasoconstrictor responses qualitatively identical to those produced by hypothalamic stimulation were found with activation of paraventricular nucleus and lateral reticular formation. Interruption of neuronal transmission in the medullary site blocked the response produced by activation of hypothalamic site. These data demonstrate that coronary vasoconstriction mediated over the sympathetic nervous system can be elicited from an interconnected pathway that links sympathetic excitatory sites in forebrain and brainstem. (Circulation Research 1987;61(suppl II):II-42-II-46)

It is well established that direct and reflex activation of the peripheral sympathetic nervous system can increase coronary vascular resistance (CVR). These findings imply that activation of sites in the central nervous system (CNS) should also produce coronary vasoconstriction. Behavioral studies carried out in dogs have provided indirect evidence for CNS involvement in stress-induced coronary vasoconstriction. Moreover, human studies have linked mental activity to transient episodes of coronary vasoconstriction in subjects with coronary artery disease. Recent studies employing pharmacologic activation of the CNS have begun to explore more directly the role of the brain in regulating CVR; however, little is known about specific sites in the brain that are capable of decreasing coronary blood flow (CBF). Two earlier studies, carried out in the dog, showed that stimulation in hypothalamus and medial longitudinal fasciculus transiently reduced CBF. One report identified a discrete lateral hypothalamic site in cat in which electrical stimulation evoked ischemia-like electrocardiographic (ECG) changes associated with increases in arterial pressure, heart rate, and contractility. Although coronary hemodynamics were not examined, the data suggested that coronary vasoconstriction may have precipitated the ECG changes.

Many studies have shown that electrical activation throughout the hypothalamus and the medulla produces pressor, positive inotropic, and positive chronotropic responses. Whether stimulation in these areas produces changes in coronary vasomotion other than the anticipated metabolically induced vasodilation has not been investigated.

Taken together, evidence demonstrating that coronary vasoconstriction can be produced by 1) direct activation of the postganglionic sympathetic cardiac nerves, 2) reflex activation of the sympathetic nervous system, 3) pharmacologic activation of the CNS, and 4) exposure to stress induced by aversive conditioning paradigms or by performance of mental tasks (in humans) indicates that the central origins of the sympathetic innervation to the heart probably play a role in neurogenically mediated increases in CVR. Based on this evidence and the knowledge that the hypothalamus is a central site for integration of cardiovascular control, studies were undertaken to determine whether focal electrical stimulation in discrete sites in the CNS could produce coronary vasoconstriction.

Materials and Methods

General Preparation

Studies were carried out in chloralose-anesthetized, open-chest cats instrumented with carotid arterial catheters for measurement of arterial pressure and heart rate. A vascular occluder was loosely secured around the descending thoracic aorta to allow later experimental manipulation of aortic pressure to mimic the pressor response to CNS stimulation or to offset depressor...
responses. CBF velocity was measured with a specially
designed pulsed Doppler flow probe previously de-
scribed\(^{23}\) that consists of a 20-MHz piezoelectric crys-
tal housed in a Silastic suction cup. The probe was
attached to the left anterior descending artery by a
vacuum. Hindquarter blood flow (HBF) velocity was
measured using a Silastic cuffed pulsed Doppler flow
probe held in place around the isolated femoral artery
with a 6-0 silk ligature.

Zero blood flow velocity was determined by switch-
ing off the Doppler receiver (electronic zero blood
flow velocity) and by occluding the coronary and fem-
oral arteries (occlusive zero blood flow velocity).
Since the blood flow velocity (kHz shift) relative to
zero blood flow velocity was known, relative changes
in velocity produced by interventions (i.e., CNS stimu-
lation) could be determined. Percent changes in vas-
cular resistance were calculated from the quotient of
mean arterial pressure and regional blood flow veloci-
ties (relative Doppler shift).

Previous studies from our laboratories carried out in
dogs have shown that over a wide range of flows and
conditions, changes in mean CBF velocity measured
with a Doppler probe correlate well \(r = 0.97\) with
changes in flow measured by electromagnetic flow-
meter, venous outflow collection, and myocardial per-
fusion with microspheres.\(^ {22}\)

Electrical Stimulation in the Central Nervous System

Tungsten monopolar microelectrodes (tip diameter,
50 \( \mu \)) were stereotaxically implanted in specific brain
sites described by coordinates adapted from the atlas of
Bleier\(^ {23}\) or Snider and Niemer.\(^ {24}\) Constant current cath-
odal pulses were delivered over 10 seconds and moni-
tored oscillographically. Mapping studies of the hypo-
thalamus and medulla were carried out in the presence
of \( \beta \)-adrenergic receptor blockade (propranolol, 1
mg/kg i.v.) to minimize changes of myocardial meta-
abolic demands.

At the conclusion of each experiment, the cats were
killed with an overdose of chloralose, the brains were
perfused, and electrode tip placements were verified
histologically.

Results

Electrical Stimulation in the Hypothalamus

Constant current electrical stimulation in a discrete
site in the lateral hypothalamus (LH) increased heart
rate (HR) \((16 \pm 4 \text{ beats/min})\), arterial pressure (AP)
\((7 \pm 2 \text{ mm Hg})\), and CBF \((11 \pm 5\%\) and transiently
decreased \((-51 \pm 5\%\) and then increased HBF
\((37 \pm 8\%\) in 71 cats.\(^ {25}\) Propranolol, administered to
minimize myocardial metabolic demands produced by
hypothalamic stimulation, abolished the tachycardia but
did not significantly alter the pressor response. \( \beta \-
Adrenergic receptor blockade unmasked a transient
decrease in CBF \((-30 \pm 5\%\) and a corresponding in-
crease in CVR \((42 \pm 7\%\). The maximum decrease in
CBF had latency to onset of 1–3 seconds, was max-
imum at 4–6 seconds, and lasted 5–30 seconds.

Ipsilateral stellate ganglionectomy not only abol-
ished the decrease in CBF produced by hypothalamic
stimulation but also unmasked an increase, presum-
ably metabolically induced by the increase in AP. In
contrast, excision of the contralateral stellate ganglion
had no effect on the coronary vasoconstriction. Fur-
thermore, intravenous \((0.25–0.5 \text{ mg/kg})\) and intracor-
ony \((30 \mu \text{g/kg})\) administration of prazosin abolished the
decrease in CBF.\(^ {23}\)

In 20% of the cats tested, electrical stimulation be-
fore propranolol resulted in an increase in HR, an
increase in CBF, and no change in AP. In these ani-
mals, \( \beta \)-adrenergic receptor blockade unmasked a de-
pressor effect produced by hypothalamic stimulation
that began 1 second after the onset of the decrease in
CBF. Propranolol administration prevented the stimu-
lation-induced tachycardia but did not alter the hind-
quarter vasoconstriction. To determine whether CBF
passively followed AP or was actively decreased by
hypothalamic stimulation, the hydraulic occluder
around the aorta was partially inflated to offset the
depressor response, and stimulations were repeated. In
all cats tested \((n = 9)\), when the aorta was partially
occluded to offset the depressor response (recorded
proximally from the carotid artery), CBF still de-
creased, and the increase in CVR was not changed, as
shown in 1 representative cat (Figure 1). The apparent
greater decrease in hindquarter flow shown in this fig-
ure is probably attributable to restriction of flow by the
aortic occluder. The mean values for the increase in
CVR were \(30 \pm 12\%\) and \(33 \pm 14\%\) before and after,
respectively, the depressor response was offset by aor-
ic occlusion. The sites in which hypothalamic stimu-
lation decreased CBF and AP were not distinct from
sites in which stimulation decreased CBF and con-
comitantly increased AP as histologically verified
(Figure 2). In 1 cat tested, ipsilateral stellate ganglion-
ectomy abolished the coronary vasoconstriction and
subsequent depressor response.

To identify other potential sites in which electrical
stimulation might produce coronary vasoconstriction,
the retrogradely transported fluorescent dye, fast blue,
was injected in the active site in the LH. Significant
labelling of cell bodies occurred in the ipsilateral para-
ventricular nucleus (PVN).\(^ {26}\) Electrical stimulation in
the PVN produced a frequency-dependent decrease in
CBF in the presence of \( \beta \)-adrenergic receptor blockade
that was similar in magnitude and duration to that
produced in the LH.

Electrical Stimulation in the Lateral Reticular Formation

Subsequent mapping studies in the medulla identi-
ﬁed an area in the lateral reticular formation (LRF) in
which stimulation in the presence of \( \beta \)-adrenergic re-
ceptor blockade decreased CBF.\(^ {27}\) While the increase
in CVR was similar in time of onset, magnitude, and
duration in contrast with the LH response pattern, the
accompanying pressor response was greater \((41 \pm 6
\text{ mm Hg})\), and the hindquarter vasoconstriction was not
followed by a secondary vasodilation.
Heart Rate (beats/min)

Mean Arterial Pressure (mmHg)

Coronary Blood Flow (kHz)

Splanchnic Blood Flow (mL)

Stimulation

Stimulation with Aortic Occlusion

FIGURE 1. Left panel: Representative example in which hypothalamic stimulation (600 μA, 0.5 msec, 100 Hz) in the presence of β-adrenergic receptor blockade decreased coronary blood flow (increased coronary vascular resistance) 1 second before decreasing arterial pressure. When depressor effect was offset by partial aortic occlusion, decrease in coronary blood flow was intact as was increase in coronary resistance. Right panel: Decrease in hindquarter blood flow appeared larger because aortic occluder inflated 1 second after the onset of stimulation simultaneously restricted blood flow to hindquarters. Sites in which stimulation-induced depressor effects were produced are indicated in Figure 2.

Neuroanatomic Studies

To determine whether the active sites in the forebrain and brainstem were anatomically connected, horseradish peroxidase–wheat germ agglutinin conjugate (HRP–WGA) was injected in the LH site. The retrograde tracer, fast blue, was injected in the site in the medulla. Anterogradely transported HRP–WGA identified descending efferent fibers in the ventrolateral forebrain and midbrain that swept dorsomedially to terminate diffusely in the ipsilateral periaqueductal gray (PAG). Retrogradely transported tracer injected in the brainstem site associated with coronary vasoconstriction labelled cell bodies in the caudal PAG in sites that overlapped terminal fields of the LH projections.

In subsequent studies, the local anesthetic lidocaine was injected in the site in the medulla associated with coronary vasoconstriction to determine whether the two sites were functionally connected. Pharmacologic interruption of neuronal transmission in the brainstem site reversibly abolished the coronary vasoconstriction produced by stimulation in the LH but spared the hindquarter vasoconstriction.

Discussion

This work has identified 3 brain sites: A discrete area in the LH, the hypothalamic paraventricular nucleus, and an area in the lateral reticular formation in which electrical stimulation in the presence of β-adrenergic receptor blockade decreased CBF (Figure 3). The coronary vasoconstriction in all 3 areas was generally accompanied by pressor and hindquarter vasoconstrictor responses; however, the increase in AP in the brainstem was greater. Unique to the LH, in 20% of the animals, electrical stimulation resulted in a decrease in AP that began 1 second after the onset of the decrease in CBF.

The coronary vasoconstriction produced by hypothalamic stimulation appears not to be part of a generalized sympathetically mediated vasoconstriction that has been evoked from sites throughout the hypothalamus or medulla for several reasons. First, in the LH,
coronary vasoconstriction occurred independently of increases or decreases in AP. Second, the region in the LH in which electrical stimulation decreased CBF was more discrete than the area in which stimulation produced hindquarter vasoconstriction, which suggests the possibility that the neurons that are capable of decreasing CBF may exist in a circumscribed area among more diffusely distributed neurons that are capable of increasing hindquarter vascular resistance. Third, stimulation in many sites in the medulla significantly increased AP and hindquarter vascular resistance with no neurally mediated changes in coronary resistance. Presumably, only a subset of these neurons is capable of decreasing CBF when electrically stimulated.

The finding that hypothalamic stimulation in the presence of β-adrenergic receptor blockade constricted coronary and femoral arteries and yet decreased AP in some animals was surprising. These data suggest the possibility that activation of specific sites in the forebrain may produce differential regional sympathoexcitation and sympathoinhibition (e.g., sympathoinhibition and vasodilation in other vascular beds whose flow was not recorded). Both this explanation and an explanation based on a depressor effect mediated by active vasodilation (e.g., cholinergic vasodilation) seem unlikely. The coronary vasoconstriction always preceded the fall in AP, and both responses were eliminated by cardiac sympathetic denervation. These data indicate that the coronary vasoconstriction was mediated by the sympathetic nerves and further suggest the alternative possibility that the decrease in CBF produced local myocardial effects to transiently diminish cardiac output and AP. Any active vasodilator response would be most likely seen in muscle beds (which instead exhibited constriction) and would be unlikely to be eliminated by relatively selective cardiac sympathetic denervation.

The neuroanatomic studies did not indicate monosynaptic connections between the sites in the LH and medulla associated with coronary vasoconstriction. However, the caudal PAG, particularly the ventrolateral portion, may be the common connection between the sites in the forebrain and the brainstem in which stimulation decreases CBF since efferent projections from the LH and afferent projections from the medulla were traced to this site. Pharmacologic interruption of neuronal transmission with lidocaine in the ipsilateral ventrolateral medulla selectively and reversibly abolished the coronary vasoconstriction produced by hypothalamic stimulation. These data provide functional evidence that the two sites are part of the same neural circuitry in the CNS that mediates the increase in coronary resistance. The persistence of the hindquarter vasoconstriction when the coronary response to hypothalamic stimulation was abolished by lidocaine suggests that either the fibers capable of mediating coronary and hindquarter vasoconstriction are anatomically separate in this region of the brainstem or that if some hindquarter vasoconstrictor fibers do course with the coronary vasoconstrictor fibers, they do not contribute significantly to the hindquarter vasoconstrictor response.

The identification of specific sites in the brain in which electrical stimulation produces coronary vasoconstriction suggests that neurons in these areas may be potentially activated by synaptic mechanisms. Based on what is known about the anxiety of exertional angina and stress-induced episodes of myocardial ischemia, it seems possible that synaptic input from higher brain centers could activate these neurons in the forebrain and brainstem. Impulses may be transmitted by a neural circuitry connecting the sites associated with coronary vasoconstriction in the hypothalamus and medulla to impinge on preganglionic sympathetic neurons in the spinal cord to ultimately activate peripheral postganglionic nerves. This work raises the possibility that this site in the LH or synaptic input to this site might selectively activate the specific coronary vasomotor fibers suggested by Juhasz-Nagy and Szentivanyi that exist in the cardiac sympathetic nerves to
ultimately mediate a coronary vasoconstriction in the absence of other cardiovascular effects.

References


Key Words • hypothalamus • coronary vasoconstriction • sympathetic nerves • α-adrenergic receptors • brainstem
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