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Full Papers

γ-Aminobutyric acid and cardiovascular function

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Summary. Evidence supporting the hypothesis that GABA-ergic mechanisms are involved in controlling mammalian cardiovascular function has been reviewed and analyzed. In vivo and in vitro studies with GABA-agonists and GABA-antagonists have revealed that activation of GABA-receptors is involved in the control of blood pressure and heart rate. Further studies conducted with agents that modify central and/or peripheral GABA-ergic systems could lead to the discovery of drugs that might be useful for treating certain cardiovascular disorders in man, such as hypertension and stroke, and should increase our understanding of the pathophysiological bases of such disorders.

It is becoming increasingly evident that the inhibitory neurotransmitter γ-aminobutyric acid (GABA) is significantly involved in the control of various physiological mechanisms and types of behavior[22,39,47]. Recent evidence supporting the hypothesis that GABA-ergic mechanisms are involved in the regulation of cardiovascular function in mammals, including man, will be reviewed here. An effort will be made to indicate processes that involve activation of classic, bicuculline-sensitive ($GABA_A$) receptors or bicuculline-insensitive ($GABA_B$) receptors, and the possible therapeutic significance of GABA-ergic agents that alter cardiovascular mechanisms will be emphasized.

Central effects of GABA-agonists and GABA-antagonists on blood pressure and heart rate

1. Studies with GABA-agonists; involvement of $GABA_A$-receptors

I.v., intracerebral (i.c.), and intracerebroventricular (i.c.v.) administration of GABA, potent GABA-agonists (e.g., muscimol), or GABA-α-oxoglutarate transaminase (GABA-T) inhibitors produce decreases in arterial pressure and heart rate in mammals by reducing sympathetic outflow from the medullary area of the brain[4,5,11,34,43,71,81,82]. Other potent GABA-agonists, such as 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol (THIP), given i.c.v. (but not parenterally), or the GABA 'prodrugs' isoguvacine propyl ester and isoarecaidine propyl ester, given i.v. or i.a., also produce hypotension and bradycardia in chloralose-anesthetized cats[33,57,64]. As such effects can be reversed by the GABA-antagonists bicuculline and picrotoxin[4,5,11,34,43,71,81,82], $GABA_A$-receptors are likely to be involved. Furthermore, as GABA (i.c.v.)-induced hypotension in pentobarbital-anesthetized dogs was reduced by pretreatment with cocaine or phentolamine and reversed to a hypertensive response by pretreatment with reserpine, this action of GABA appears to involve a release of endogenous norepinephrine (NE)[23].

I.c.v.-administered muscimol also reduced blood pressure, heart rate and sympathetic outflow in conscious or anesthetized spontaneously-hypertensive rats (SHRs), and the magnitude of this hypotensive effect of muscimol tends to exceed that of clonidine; like clonidine, muscimol exerted negligible orthostatic effects in doses that produced pronounced hypotension[7]. Since the SHR represents a model for essential hypertension, centrally-active GABA-ergic agents might be useful in controlling essential hypertension in man. As daily injections of the GABA-T inhibitor valproate (100 mg/kg, i.p.) reduced the development of DOCA-salt hypertension in rats (an effect that became significant during the 4th week of treatment)[59], GABA-ergic agents also appear to be effective in experimental models of hypertension (see also Takahashi et al.[70].

Although i.c.v.-injected muscimol produces hypotension in SHRs (see above), no differences in Na^+-independent [^{3}H]-muscimol binding parameters were evident between membrane particles prepared from cerebellum, pons-medulla or forebrain of SHR and normotensive (WKY) rats during the development of hypertension[17,73]. However, the densities of both Na^+-independent and Na^+-dependent binding sites for [^{3}H]GABA were decreased in membranes prepared from the cerebral cortices of SHR as compared to WKY[75]. Further, with regard to this genetic component of hypertension, Tunnicliff[74] has shown that both Na^+-dependent [^{3}H]GABA binding (related primarily to GABA uptake) and synaptosomal Na^+-dependent [^{3}H]GABA uptake in the cerebral cortex were negatively correlated with blood pressure in 5 inbred mouse strains, but that Na^+-independent [^{3}H]GABA binding (related primarily to neuronal GABA-receptors) was only poorly correlated with blood pressure.

2. Studies with baclofen; possible involvement of $GABA_B$-receptors

Baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid; Lioresal®) is a lipophilic analogue of GABA which might act at bicuculline-insensitive GABA-receptors ($GABA_B$-receptors) in the CNS[14]. This agent generally produces hypotension when administered to man[55] or to anesthetized experimental animals[48,54,65,69]. However, Chahl and Walker[19] have shown, in anesthetized rats, that although i.v.-administered baclofen produced transient decreases in blood pressure and heart rate at low doses ($< 5 \times 10^{-8}$ mole), it produced more pronounced increases in both parameters at higher doses ($> 5 \times 10^{-7}$ mole). Also, in conscious rats, i.p. (5 mg/kg) or i.c.v. injections of baclofen produced sustained hypertension and tachycardia, and as such actions of baclofen were reversed by phenoxybenzamine pretreatment and attenuated following catecholamine depletion by means of DL-α-methyl-m-tyrosine, noradrenergic mechanisms (regulated by $GABA_B$-receptors) might have been involved[52]. The reason for this discrepancy between the results obtained in anesthetized vs conscious animals is probably related to the actions of barbiturate anesthesia and/or to species differences[13,53]. In this regard, it is noteworthy that Bousquet et al.[13] have shown that i.c.v. administration of baclofen produced marked hypotension and bradycardia in the conscious rabbit.

Hypertension produced by i.p.-administered baclofen in the conscious rat might be due to its action in the nucleus tractus solitarii (NTS)[51], which is situated in the dorsal medulla oblongata. In this regard, it should also be noted that microinjections of GABA or muscimol, as well as baclofen, into the NTS of pentobarbital-anesthetized cats elicited hypertension and tachycardia[12]. As the effects of muscimol, but not those of baclofen, were prevented by prior injection of bicuculline into the same site[12], both $GABA_A$ and $GABA_B$-receptors might be involved in controlling the baroreceptor reflex pathway within the NTS[12,32,50]. I.c.v. injection of baclofen (20 µg) in pentobarbital-anesthetized cats elicited marked hypertension[11]. This effect was not antagonized by bicuculline-methiodide (i.c.v.), indicating that $GABA_B$-receptors had been activated. However, as this effect was prevented and reversed by i.c.v.-injected glutamate (1 mg/kg) or kainic acid (1 µg/kg), it was suggested that baclofen might selectively inhibit glutamate release within forebrain (e.g., hypothalamic) structures that are involved in cardiovascular regulation[11]. Other studies have indicated that baclofen has direct inhibitory and remote disinhibitory effects[41,42].

3. Studies with GABA-antagonists

Systemic, i.c. or i.c.v. injections of picrotoxin (which might act by blocking GABA-associated Cl^--ionophores) and bicuculline (a directly-acting GABA-antagonist) also influence cardiovascular function in mammals[10,25,61,77]. These GABA-antagonists can elicit hypertension and tachycardia or hypotension and bradycardia, depending upon the dose and route (or i.c. site) of administration that is used (e.g., hypertension after i.c.v. administration of picrotoxin[77]; hypotension after i.a. injection of picrotoxin or bicuculline[25]). Hypertension and tachycardia produced by picrotoxin are probably due to an increased sympathetic outflow to the cardiovascular system[26,56,77], whereas hypotension and bradycardia produced by picrotoxin or bicuculline are probably related to vagal activation[25]. DiMicco and Gillis[25] have provided evidence that both of these GABA-antagonists act in forebrain areas by stimulating sympathetic structures and in the medulla-pons area by stimulating parasympathetic structures. Post-injection time is also important in relation to the cardiovascular effects of GABA-antagonists; e.g., it has been shown that i.v.-administered picrotoxin and bicuculline exert biphasic effects; initial hypotension and bradycardia, followed by hypertension and tachycardia[25,26]. Decreases in blood pressure and heart rate produced by i.a. injection of picrotoxin or bicuculline in the cat were reversed by muscimol[25]. Unlike GABA-agonist-induced bradycardia, which is probably caused by a reduction of sympathetic outflow from the medulla (see above), GABA-antagonist-induced bradycardia is probably caused by stimulation of parasympathetic function (i.e., by blockade of inhibitory GABA-ergic synapses - a disinhibitory mechanism) and mediated by the vagus nerves[24]. As injections of bicuculline-methiodide directly into the nucleus ambiguus of the cat led to marked hypotension and bradycardia, and as these effects were reversed by muscimol, this brain stem site might be responsible for GABA-mediated inhibition of vagal outflow[24].

Peripheral effects of GABA-agonists and GABA-antagonists on blood pressure and heart rate

1. In vivo studies

About 24 years ago, Elliott and Hobbiger[29] observed that peripherally-administered GABA (1.0 mg/kg, i.v.) induced transient hypotension and bradycardia in dogs. As such effects of GABA were not reversed by bilateral vagotomy or by atropine, these workers proposed that GABA might have acted on peripheral sympathetic ganglia. This suggestion has been supported by the studies of Stanton and Woodhouse[66] and by the more recent studies of Billingsley et al.[9] and Billingsley and Suria[8], which showed that administration of GABA in doses that are not expected to cross the blood-brain barrier (i.e., 1-1000 µg/kg, i.v.) induced short-lasting (< 10 min), picrotoxin-sensitive hypotension and bradycardia in ethrane-, chloralose-,

or pentobarbital-anesthetized dogs or rats. These workers postulated that GABA might have produced such effects by acting directly on vascular, cardiac and lung tissue[8], a hypothesis which is supported to some extent by the in vitro studies that are discussed below.

2. In vitro studies

Strips of canine basilar and middle cerebral arteries were relaxed by GABA (10^{-7}–10^{-5} M), and this action was antagonized by pretreatment with 10^{-5} M picrotoxin[31]. Some specificity of this action was evident, since GABA did not relax dog or rabbit aorta, mesenteric artery, or portal vein, and since glycine or glutamate (10^{-8}–10^{-5} M) did not produce relaxation of cerebral arteries[31]. Other studies revealed that the relative potencies of various GABA-agonists in relaxing cerebral arteries were consistent with their depressant effects on mammalian central neurones; the concentration of GABA required to produce 50% of maximal response (EC_{50}) was 8×10^{-7} M for vasodilatation of cat middle cerebral arteries[27,37]. [^{3}H]Muscimol was bound to membranes of bovine cerebral blood vessels by a high-affinity process (K_B, or dissociation constant $\simeq 4\times10^{-8}$ M), and this binding was inhibited by GABA-agonists and by bicuculline with relative potencies that were consistent with those found for GABA-receptors of mammalian brain[38]. Such cerebrovascular GABA-receptors might mediate the increases in cerebral blood flow and brain tissue O_2 tension that have been produced by administration of GABA or muscimol to mammals[28,44].

In rabbit basilar arteries that had been previously contracted with 5-HT, GABA (but not baclofen) produced relaxation with $EC_{50}\simeq 2.4\times10^{-5}$ M, and this response was inhibited by pretreatment with bicuculline (3×10^{-7} and 3×10^{-6} M) or picrotoxin (10^{-7}–10^{-6} M), indicating an involvement of $GABA_A$-receptors[6]. However, as both GABA and baclofen reduced the contractile response produced by transmural electrical stimulation by a mechanism that was insensitive to bicuculline, $GABA_B$-receptors might also be present in rabbit basilar artery[6]. In this regard, it should also be noted that addition of GABA (up to 10^{-3} M) to the superfusion medium did not affect basal release of pre-loaded [^{3}H]NE, but did lead to a decrease in electrically-evoked [^{3}H]NE release from rat isolated atria[15]; the receptor involved, considered to be a presynaptic $GABA_B$-receptor present on sympathetic nerve endings, was not sensitive to bicuculline-methochloride or picrotoxin, but was activated by baclofen (see also Bowery et al.[14], see above). More recently, both $GABA_A$ (bicuculline-sensitive) and $GABA_B$ (bicuculline-insensitive) binding sites have been detected in cryostat sections of rat atria using ligand-binding methods[16]. As binding to both $GABA_A$ and $GABA_B$ sites was abolished or reduced by chronic pre-treatment of the rats with 6-hydroxydopamine, it was concluded that these binding sites are on adrenergic nerve fibers[16]. GABA (10^{-6}–10^{-3} M) also decreased electrically- or high-K^+ evoked [^{3}H]NE release from strips of rabbit pulmonary artery by an action that was insensitive to picrotoxin or bicuculline-methiodide[67]. Taken together, these studies indicate that the hypotensive action of systemically-administered GABA could involve, at least in part, presynaptic inhibition of postganglionic sympathetic transmission to the heart and blood vessels via activation of baclofen-sensitive $GABA_B$-receptors[67].

With further regard to peripheral effects of GABA-ergic agents, it should be noted that mammalian whole blood contains about 0.5–1.3 μM GABA, and that the level of blood GABA in rats is increased after administration of GABA-T inhibitors[30]. Although the GABA level of blood is very low (compared to CNS levels), it has been suggested that blood-borne GABA might be involved in regulating synaptic transmission in some sympathetic ganglia, perhaps by decreasing the release of excitatory neurotransmitter[36]; i.e., possibly by an action on $GABA_B$-receptors (see above). GABA-T activity is present in cerebral blood vessels[76] and in blood platelets of mammals[79], and the GABA-synthesizing enzyme glutamate-α-decarboxylase (GAD) is also present in cerebral blood vessels[40,45,58].

GABA and human cardiovascular function

From the foregoing discussion, it seems possible that GABA-ergic systems are involved in some human cardiovascular disorders. Although no established facts exist to support this contention, it is noteworthy that GABA administration has been shown to decrease blood pressure in hypertensive human subjects[62], that cerebrospinal fluid GABA levels were elevated in patients with thrombo-embolic occlusive cerebrovascular disease, vertebral basilar ischaemia, or during migraine attacks[2,78], and that orally-administered GABA (3 g/day for 8 weeks) was more effective than pyrithioxine (600 mg/day for 8 weeks) or placebo in treating certain cerebrovascular disorders[49]. In this latter study, GABA administration also reduced the psychological symptoms that accompanied cerebral infarction and cerebral hemorrhage in human subjects[49], leading one to consider the coupling that appears to exist between certain central GABA- and benzodiazepine-receptors[20,72] and the fact that benzodiazepines have been prescribed for cardiovascular disorders (e.g., hypertension)[35,80]. In this regard, it might be noted that benzodiazepines, like GABA (see above), can produce decreases in central sympathetic outflow and blood pressure in experimental animals[3,18,63], and that chronic administration of diazepam (commencing in the neonatal period) to SHRs can offset the development of hypertension[60].

Concluding remarks

GABA-ergic systems (involving $GABA_A$- and perhaps $GABA_B$-receptors) appear to be involved in controlling cardiovascular function in mammals. Systemically-administered GABA-agonists produce hypotension and bradycardia by reducing central sympathetic outflow and by activating peripheral GABA-receptors that appear to exist in cardiac and vascular tissues. The possible therapeutic significance of such observations is obvious when one considers that cerebral changes are primary factors involved in the production of arterial hypertension by emotional stress[21,68]. Further research with GABA-ergic substances that penetrate into the CNS and with others that do not penetrate into the CNS (but which are also not rapidly metabolized) might lead to the development of new drugs for treating cardiovascular disorders of man. In this regard, it seems that GABA-agonists might be more useful than GABA-antagonists as possible anti-hypertensive agents since the hypotensive effects of GABA-antagonists appear to be less pronounced and generally followed by pronounced hypertension and tachycardia (see, e.g., DiMicco and Gillis[25] and DiMicco et al.[26]; see above). It might be best to conduct such studies in unanesthetized animals since certain general anesthetics (e.g., pentobarbital, α-chloralose) can mimic or enhance the actions of GABA[42,46].

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