Role of α_2-Adrenergic Receptors in Hypertension

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This is a brief review of a series of experiments conducted over the past two decades, exploring the role of the α_2-adrenergic receptors (α_2-AR) in salt-induced hypertension. The data suggest that salt loading alters the activity of central α_2-AR, resulting in a hypertensive hyperadrenergic state. Studies to separate the role of each α_2-AR subtype (α_{2A}, α_{2B}, and α_{2C}) have used genetically engineered mice with disrupted genes for each subtype, or gene treatment in rats with antisense-oligodeoxynucleotides targeting a specific gene sequence. Taken together, the results of these studies indicate that the α_{2A}-AR is centrally predominant and exerts a tonic sympathoinhibitory function, whereas peripherally it has a vasoconstrictive effect; the α_{2B}-AR is responsible for the central hypertensive sympathoexcitatory response to salt, but is not expressed on vascular wall structures; and the α_{2C}-AR seems to have no hemodynamic function. Am J Hypertens 2001;14:171S–177S © 2001 American Journal of Hypertension, Ltd.

Key Words: Salt-dependent hypertension, α_2-adrenergic receptor subtypes, sympathoexcitation, sympathoinhibition, gene treatment.

The sympathetic nervous system (SNS) is a major contributor to the pathogenesis and maintenance of hypertension. To a large extent, the hypertensive effects of the SNS are exerted through activation or inhibition of α_2-adrenergic receptors (α_2-AR). There are three subtypes of α_2-AR—α_{2A}, α_{2B}, and α_{2C}—that have been cloned in recent years. However, pharmacologic experiments and radioligand-binding studies lack the selectivity to differentiate these subtypes and define their functional characteristics. This has only become possible with genetic engineering to produce mice with deleted or mutated genes for each one of the α_2-AR subtypes, thus permitting dissection of their specific functions.

Our interest in the function of α_2-AR originated from studies exploring the mechanisms by which salt excess raises blood pressure (BP). The accumulated evidence pointed to stimulation of a number of vasoconstricting mechanisms, leading to increased systemic vascular resistance, regardless of whether it is accompanied by changes in intravascular or extracellular fluid volume.[1] During the past two decades we have conducted a series of experiments with acute or chronic salt loading in anephric or subtotally nephrectomized animals, respectively, in an effort to elucidate the hemodynamic and humoral characteristics of salt-induced hypertension.[2–9] The data suggest that acute BP increase is due to vasoconstriction mediated in its earliest phase partly by excess release of arginine-vasopressin (AVP) and partly by excessive sympathetic stimulation. In the established phase of salt-dependent hypertension, the prevalent mechanism is a hyperadrenergic state induced by alterations in the α_2-AR of the central SNS leading to diminished sympathoinhibitory activity. A series of experiments using stereotaxically guided microinjections of hypertonic saline in specific nuclei of the brainstem[10–14] further confirmed this interpretation, and suggested that this is an ionic effect of NaCl, as isovolumic equiosmotic solution of dextrose or LiCl produced no such effect. A critical appraisal of our experimental evidence, as well as that of other investigators in the field[15–21] was published as an editorial review in 1989[22] and helped reinforce our belief that α_2-AR play a pivotal role in this type of hypertension. Specifically, we proposed the hypothesis that sodium decreases the affinity of central presynaptic sympathoinhibitory α_2-AR for naturally occurring agonists, thus resulting in sympathetic disinhibition and increase in sympathetic outflow. The end result is elevated systemic BP characterized by a hyperadrenergic state.

Tissue Expression of the α_2-AR Genes in Normotension and Hypertension in the Rat

In a subsequent series of studies, we sought to further define the expression of α_2-AR in brain and other tissues and their function in hypertension.[23–32] The results of

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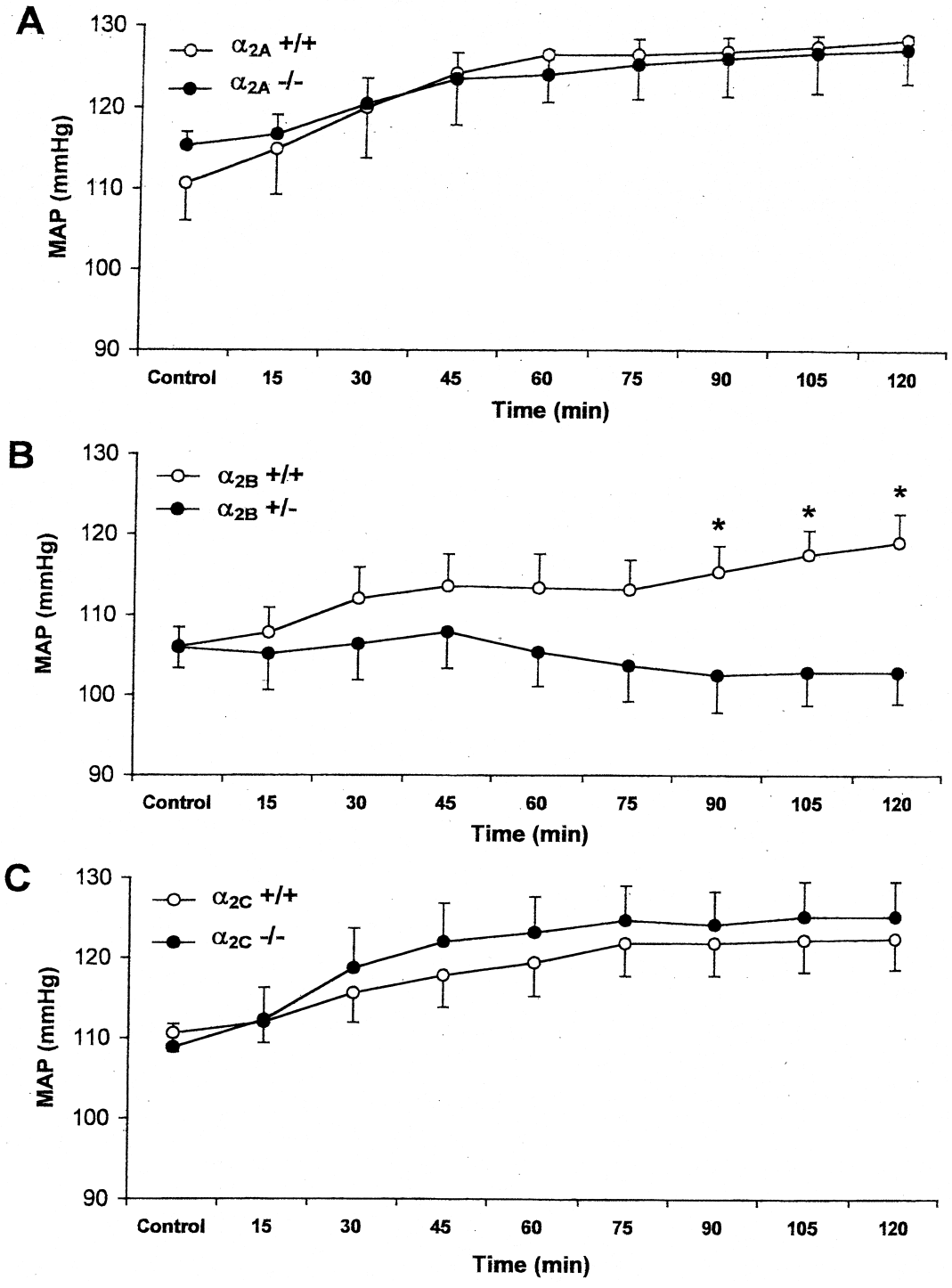

FIG. 1. Mean arterial pressure during a 2-h hypertonic saline infusion in genetically engineered or wild-type anephric mice. *$P < .05$ between α_{2B}-adrenergic receptor deficient and wild-type mice. (Adapted with permission from Lippincott Williams & Wilkins for Makaritsis et al: Role of α_2-adrenergic receptor subtypes in the acute hypertensive response to hypertonic saline infusion in anephric mice. Hypertension 2000;35:609–613.)

these studies, which have elucidated a number of differences in the distribution of α_2-AR subtype gene expression in various brain and other tissue regions between hypertensive and normotensive rats, are summarized.

We have been particularly interested in defining the exact location of the α_2-AR subtypes in various structures of the brain, especially regions that may be involved in cardiovascular control. In situ hybridization has allowed us to map subtype expression in brain structures from 12-week-old, spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) rats, at which time the SHR (which are considered to be a counterpart to human

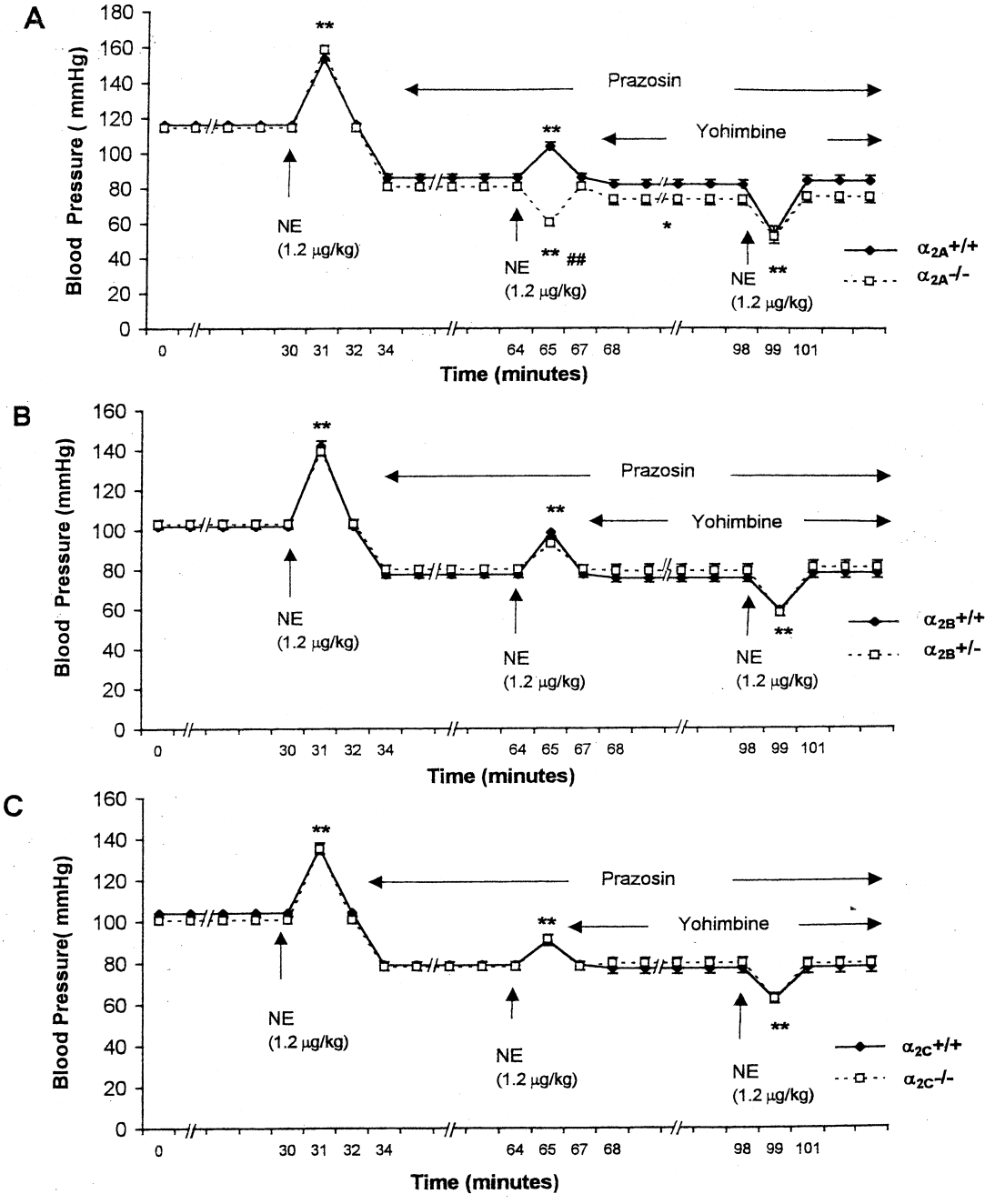

FIG. 2. Blood pressure responses to norepinephrine bolus injections during sequential blockade of α_1- and α_2-adrenergic receptors in genetically engineered or wild-type mice. (Adapted with permission from Elsevier Science Inc. for Duka et al: Role of the postsynaptic α_2-adrenergic receptor subtypes in catecholamine-induced vasoconstriction. Gen Pharmacol: The Vascular System 2000;34:101–106.) $*P <$ .05, $**P <$ .01 from baseline, $\#\#P$ .01 between α_{2A}-adrenergic receptor deficient and wild-type mice.

essential hypertension), were already hypertensive (systolic BP for SHR was 183 ± 3 *v* 116 ± 4 mm Hg for WKY). With the use of the Inquiring Densitometry system, brain sections from SHR and WKY were processed with a subtype-specific α_2-AR probe, exposed on a single piece of Hyperfilm (Amersham) and digitized. In this manner relative expression of each α_2-adrenergic receptor subtype mRNA was assessed on these sections, beginning with examination of pons–medulla structures such as the locus coeruleus, nucleus tractus solitarrii, dorsal motor nucleus of the vagus, and rostral ventral lateral medulla. Our preliminary comparison of α_2-AR subtype gene expression indicates that in various regions of the brain the levels of α_2-AR mRNA differ between SHR and WKY. For example, in the cerebral cortex SHR express 34% more α_{2A}-AR mRNA and about 50% more α_{2C} mRNA than WKY, whereas in the cerebellum SHR have 25% less α_{2A}-mRNA and 37% less α_{2C} mRNA than WKY. The expression of α_{2B}-AR mRNA in cerebellum and cortex does not differ between SHR and WKY. In contrast, in the

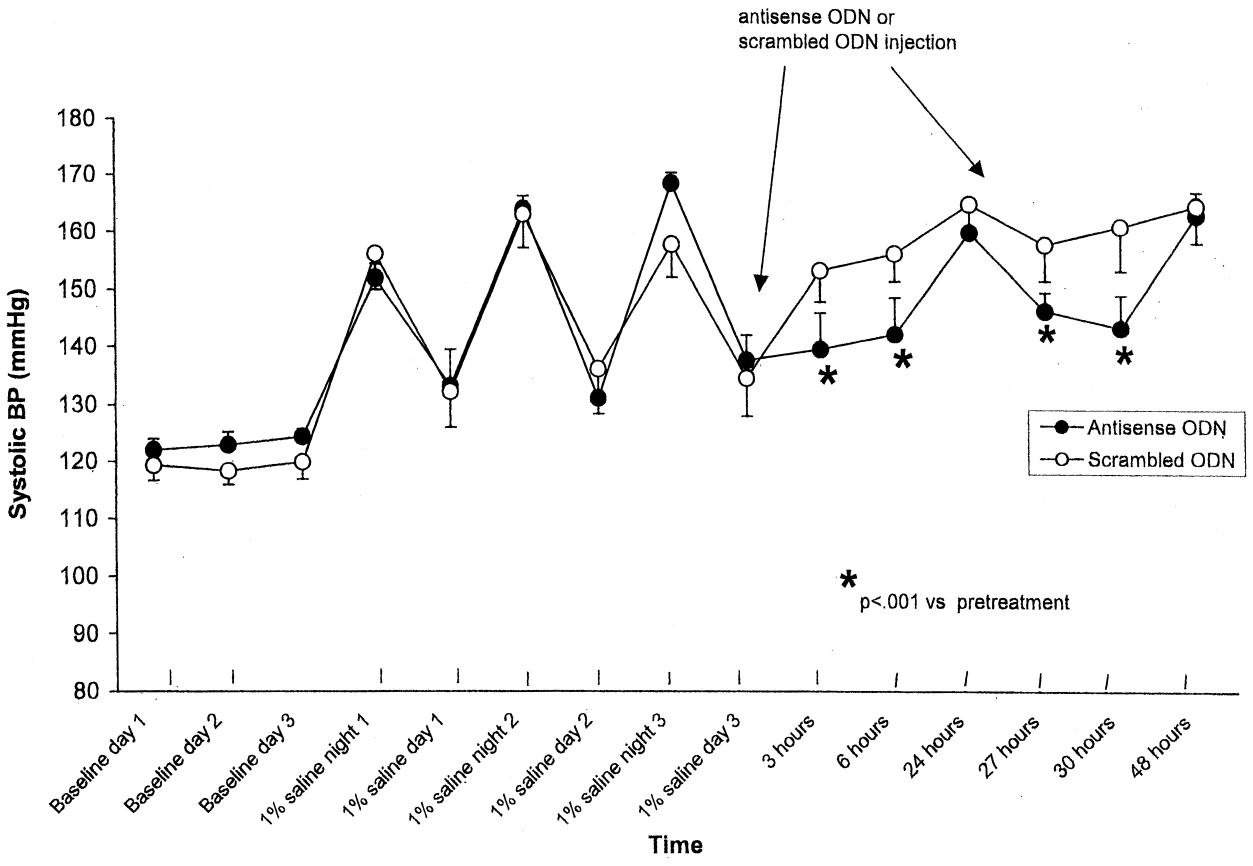

FIG. 3. Daily blood pressures during baseline, dietary salt loading, and intracerebroventricular injection of antisense (or scrambled) oligodeoxynucleotides against a chosen mRNA sequence of the α_{2B}-adrenergic receptor in rats. (Data derived from Ref. 46.)

pons–medulla SHR have 20% lower expression of α_{2A}-AR and 61% lower expression α_{2B}-mRNA than WKY. (The levels of α_{2C}-mRNA in the medulla are too low for quantitation.) The functional significance of these differences is unclear at this time. The pathogenic mechanism of hypertension in SHR has not been determined, as their BP increases with age even on a low-salt diet, it responds readily to angiotensin inhibition, and is not characterized by indices of altered sympathetic activity. Accordingly, differences in expression of central α_2-AR subtype genes may reflect compensatory responses rather then initiating mechanisms.

Similar studies were also carried out in aortic wall tissues from normal and atherosclerotic rabbits and revealed the presence of α_{2A} and α_{2C} mRNA, but no α_{2B} mRNA, indicating that the α_{2B}-AR is absent from arterial wall structures.[32]

Studies on Genetically Engineered Mice

After completion of these studies, we decided to switch our research to mice, because this species is suitable for genetic manipulations, especifically deletion of each of the α_2-AR gene subtype to better define its role in the development or maintenance of hypertension.[33] We undertook a series of such experiments in mice genetically engineered by Dr. Brian Kobilka's group at Stanford University. These researchers have succeeded to knock-out either the α_{2A}-AR, the α_{2B}-AR, or the α_{2C}-AR gene.[34–38] Using the model of subtotal nephrectomy with chronic dietary salt loading, we found that mice deficient in α_{2B}-AR (ie, heterozygotes lacking one copy of the α_{2B}-AR gene, with greatly reduced levels of the α_{2B}-AR protein), had a greatly attenuated BP response to salt loading, which never did reach hypertensive levels. On the contrary, animals lacking the α_{2A}-AR or α_{2C}-AR subtype gene developed hypertension to the same extent as their wild-type counterparts.[39,40] In fact the α_{2A}-AR gene knockout mice had already higher BP and circulating catecholamines at baseline and became hypertensive in less than 2 weeks' time, as compared to 4 or 5 weeks of salt loading required by the α_{2C}-AR knockouts and all wild-type mice. These findings are consistent with those of other investigators who suggested that central sympathetic outflow is essentially regulated through the presynaptic α_{2A}-AR subtype, which exerts a hypotensive action.[35–38] In the resting state, it appears that the α_{2A}-AR is the predominant α_2-AR subtype with a tonic sympathoinhibitory function. All of these studies, as well as our own, have suggested that the α_{2C}-AR subtype seems to have no role in BP regulation.

The novel finding that the α_{2B}-AR deficient mice are

unable to develop salt-induced hypertension could be attributable to any one of several mechanisms, for example, 1) abnormal renal handling of sodium (ie, inability to retain sodium); 2) diminished capacity to release norepinephrine by central sympathetic neurons; or 3) inability to vasoconstrict in response to circulating norepinephrine. Some investigators suggested that the α_{2B}-AR is exclusively located in the vascular wall, and its effect is that of direct vasoconstriction.[35,37] However, we have detected high density of α_{2B}-AR mRNA in areas of the brainstem,[30] but not in the arterial wall.[32] Other investigators also have been unable to detect expression of α_{2B}-AR in vascular wall tissues.[41] Besides, catecholamine-induced vasoconstriction is mainly effected through the peripheral postsynaptic α_1-AR,[42] which makes this third explanation less plausible.

To explore the other two explanations we used the acute model of salt-induced hypertension (ie, anephric animals treated with hypertonic 4% saline infusion), which we had used extensively for rats in the past,[2–4] using this time groups of anephric mice deficient for each one of the α_2-AR subtypes.[43] As expected, the α_{2A}-AR gene knockouts started from a higher BP baseline, but all five subgroups (ie, the α_{2A}-AR knockouts, the α_{2C}-AR knockouts, and their respective wild-type controls, as well as the wild-type counterpart of the α_{2B}-AR-deficient mice) developed similar acute BP elevations ranging from 12 to 18 mm Hg at the end of the 2-h hypertonic saline infusion; on the contrary, the α_{2B}-AR-deficient subgroup had an average 3 mm Hg decrease of BP at the end of that period (Fig. 1). All animals exhibited stimulated norepinephrine levels at the end of the infusion, and in all cases the α_2-AR gene-deficient subgroups tended to have higher levels than their wild-type counterparts, but this difference was significant only for the α_{2B}-AR-deficient subgroup. These findings effectively excluded both other explanations cited above: accumulation of sodium and fluid in the extracellular space was equal in all anephric animals receiving an intravenous infusion of 2 mL hypertonic 4% saline, and stimulation of norepinephrine release did occur in the α_{2B}-AR-deficient mice, even more so than in their wild-type counterparts.

This dissociation between heightened stimulation of norepinephrine release and decreasing levels of systemic BP was an unexpected and surprising finding. Coupled with our earlier findings of increased density of α_{2B}-AR mRNA in certain areas of the brainstem, which represent centers of baroreflex control (such as the nucleus tractus solitarii and locus coeruleus,[30] and inability to detect α_{2B}-AR mRNA in arterial wall).[32,41] We could offer only one plausible explanation for these data: that the α_{2B}-AR has a hypertensive function mediated through the central SNS. We propose that activation of the sympathoexcitatory α_{2B}-AR would oppose the hypotensive sympathoinhibitory effect of the α_{2A}-AR in the central SNS centers of vascular tone regulation. In such case, excessive levels of circulating norepinephrine in α_{2B}-AR-deficient mice would result in unopposed stimulation of the central presynaptic α_{2A}-AR and therefore, tend to further lower the systemic BP, which is precisely what we found in these mice. In contrast, in the α_{2A}-AR knockout mice, unopposed function of central α_{2B}-AR would lead to a hypertensive hyperadrenergic state, even at baseline. This state would be further exacerbated by the stimulus of salt-loading, as indeed was seen in the experiments with α_{2A}-AR knockouts.

Several questions need to be answered before this theory can be accepted. A crucial one is whether α_{2B}-AR-deficient mice can vasoconstrict in direct response to catecholamines. To clarify this point, we conducted infusions of α_2-AR agonists or antagonists in various combinations in the absence of each one of the α_2-AR subtypes.[44] Fig. 2 illustrates the sequence of these experiments. A bolus infusion of norepinephrine elicited, as expected, a significant BP increase in all animals, evidently mediated mainly through α_1-AR subtype stimulation.[42] After blockade of α_1-AR with prazosin, the same norepinephrine bolus produced a lesser (about one-third) pressor response in all wild-type as well as the α_{2B}-AR- and α_{2C}-AR-deficient mice, presumably through stimulation of one or both of the remainder α_2-AR subtypes; however, in the α_{2A}-AR knockouts, the same norepinephrine bolus produced a significant decrease in BP by about 20 mm Hg. This would indicate that the α_{2A}-AR is responsible for the vascular wall sympathetic vasoconstrictive response in the absence of functional α_1-AR. When both α_1-AR and α_{2A}-AR are eliminated by concurrent blockade of all α-AR types with the addition of yohimbine to prazosin, the BP remains unchanged in all groups except for the α_{2A}-AR knockouts, in which yohimbine blocks the remaining central α_{2B}-AR and thus, lowers further the systemic BP. Under these conditions, the vascular response to norepinephrine bolus in all groups is relaxation (probably by β_2-AR stimulation). These experiments indicate that the only vascular wall α_2-AR subtype capable of direct vasconstriction is the α_{2A}-AR.

Studies Using Antisense Technology in Rats

Another investigative technique that has been gaining attention in recent years to elucidate the role of various proteins is gene treatment.[45] One approach to this is the inhibition of a gene product by delivery of antisense oligodeoxynucleotides (AS-ODN) targeting a chosen sequence of the mRNA, thus arresting further translation of the gene's message. Using the AS-ODN technology, we designed a series of experiments in rats to demonstrate that induction of salt-dependent hypertension requires intact functional α_{2B}-AR in the central SNS. Rats were rendered hypertensive by subtotal nephrectomy and 1% saline as drinking water. They had then a small cannula implanted stereotaxically in the left lateral cerebral ventricle and a radiotelemetry probe for constant BP and heart rate recording implanted around the aorta. Intracerebroventricu-

lar microinjection of AS-ODN chosen to target a specific sequence of the α_{2B}-AR gene should arrest the generation of the α_{2B}-AR protein in the central nervous system of these rats for several hours. It produced a BP lowering by 30 ± 5 mm Hg compared to similarly treated rats that received scrambled ODN injection (Fig. 3). This effect on BP was accompanied by a lowering in heart rate by 82 ± 15 beats/min and behavioral changes (drowsiness, delayed righting reflex, loss of balance) peaking at 3 to 6 h after injection and wearing off gradually thereafter. By 24 h these parameters had returned to baseline, at which point a second injection of AS-ODN produced identical results, whereas repeat injection of scrambled ODN produced no changes. Injection of fluorescein-labeled AS-ODN revealed selectively increased uptake of fluorescence by several paraventricular and brainstem structures, including the optic nerve, the nucleus tractus solitarii, the locus coeruleus, as well as the cerebellum.[46] These observations corroborate the notion that induction of hypertension by salt loading is mediated by α_{2B}-AR located in central SNS neurons known to be involved in BP regulation and baroflex control.

In conclusion, these experiments suggest that the central presynaptic α_{2B}-AR is responsible for the hypertensive, hyperadrenergic response to salt loading; the α_{2A}-AR presynaptically (in the central SNS) is the predominant α_2-AR subtype and has a sympathoinhibitory function, whereas postsynaptically (on the vascular wall) it has a vasoconstrictive action. The α_{2A}-AR-mediated vasopressor response to catecholamines is qualitatively similar to, but quantitatively weaker by about 65% to 70%, than that of the α_1-AR.

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