Hypertension

α_2-Adrenoceptors in Clinical Medicine

Internal Medicine Grand Rounds

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William A. Pettinger, M.D.

Introduction

During the last few years, activation of α_2-adrenoceptors has been demonstrated to influence a wide variety of effects in various tissues. These include alteration of mood, sodium and water absorption in the gut and kidney, insulin release, fat mobilization, electrical conduction in the heart, platelet aggregation, blood pressure and many other effects. I will attempt to provide an overview of this rapidly evolving area with examples of α_2-adrenoceptor activation in several tissues, an assessment of their demonstrated and potential importance and possible clinical implications of some of these effects.

1. *Molecular effects of α_2-adrenoceptor activation.*

Let's begin with an attempt to simplify the diverse and apparently unrelated effects of activation of α_2-adrenoceptors by considering more basic aspects of this system that are common to various tissues and their functions. In each tissue in which the molecular effects of α_2-adrenoceptor activation were studied, investigators have found that they inhibit the activation of adenylate cyclase and cAMP formation (1-8). Prior to 1977, the unique characteristics (9) of α_2-adrenoceptors were unknown, even though the capacity of α-adrenoceptors to inhibit cAMP formation was known in the late sixties (1-3). The importance of cAMP as a "second messenger" in mediation of intracellular events was heralded by awarding of the Nobel Prize to Earl Sutherland for discovery of this nucleotide and some of its important effects.

Adenylate cyclase can be activated by many different hormones. Specificity of effect is governed largely by the specificity of the tissue

receptor for a given hormone that activates the adenylate cyclase. The importance of the phenomenon of specificity of receptors is emphasized by the number and qualities of effects of the various hormones which regulate renal function. Parathyroid hormone, for example, decreases bicarbonate, calcium, phosphate and sodium reabsorption in the proximal tubule. This hormone enhances calcium reabsorption and increases urinary excretion of phosphate and sodium in more distal areas of the tubule and collecting duct. These effects generally parallel parathyroid hormone's capacity to activate adenylate cyclase in these segments of the tubule as characterized in microdissection studies by Morel and others (10).

Several new perspectives have emanated from studies of α_2-adrenoceptors. 1) If adenylate cyclase has not been activated, there is no effect of α_2-adrenoceptor activation except possibly in smooth muscle tissue. 2) The qualitative effect of α_2-adrenoceptor activation is determined by the function-specific adenylate cyclase which has been activated in a particular tissue or organ. 3) While nearly all tissues have adenylate cyclase, there is a spectrum of capacities of α_2-adrenoceptors to inhibit this activation. We will address this issue to the extent that data is available when reviewing function-specific inhibition of adenylate cyclase.

In the introduction to the molecular aspects of these receptor interrelationships I should mention that there are other endogenous and exogenous substances which can mediate inhibitory signals to activated adenylate cyclase. These include adenosine, acetylcholine (muscarinic receptors), somatostatin, opiates and under some circumstances prostaglandins and ADP. These will be discussed with specific tissues in which their capacity to inhibit adenylate cyclase appears to mediate specific functions or pharmacologic effects.

A major commitment in our Department of Pharmacology is the purification of some of the proteins that are involved in adenylate cyclase regulation and characterization of their interactions as they influence rates of cAMP formation in plasma membranes. For an update on some of their recent contributions please consult references 11-13.

2. *Characteristics of α_2-adrenoceptors.*

With this background information, let me return to the beginning of my story. The function which permitted pharmacologic characterization of α_2-adrenoceptors in 1964 was the reversal of melanocyte granule dispersion or rapid color changes in the frog skin. Our lack of understanding of the molecular events resulted in a delay in publication until 1977 (14) and the proposal of a new basis for functionally classifying α-adrenoceptors (9). This classification is now generally accepted both at biochemical and pharmacologic levels (15-28). According to van Zwieten in 1980, "after a period of confusion a clear picture concerning the subdivision of α-adrenoceptors has now emerged" (21).

Abe et al., (3) using the frog skin model and Handler (2) using the toad bladder, were among the first investigators to demonstrate the relationship between adenylate cyclase-cAMP and α-adrenoceptors but as noted above, were unaware of the unique characteristics of the α_2-adrenoceptors. More recent studies using clonidine (29) have confirmed the α_2-receptor characteristics of the frog skin model (9) and reinforced our original contention (14) that the α-adrenoceptors were similar to those in the brain whereby centrally acting agents lower blood pressure (28-30).

3. *Specificity of α_2-adrenoceptor effects - Renal model.*

Let us now consider some effects of activating α_2-adrenoceptors in several tissues beginning with the kidney. This is new information obtained in our laboratory by Dr. Donald Smyth (32b). Using a highly functional isolated perfused rat kidney preparation he has demonstrated that α_2-adrenoceptor activation can cause sodium retention by the kidney. In order to demonstrate this effect on sodium excretion, he activated adenylate cyclase and stimulated sodium excretion using several interventions. The most useful one turned out to be furosemide. Infusion of epinephrine reversed the adenylate cyclase activation and enhanced sodium excretion resulting from the furosemide. This effect of epinephrine appears to be α_2-adrenoceptor mediated for two reasons. One is that in this preparation β- and α_1-adrenoceptors were blocked by propranolol and prazosin respectively and secondly, the α_2-adrenoceptor selective blocking drug yohimbine reversed the effect of epinephrine.

You will recall that the function specificity of adenylate cyclase activation is determined by the plasma membrane receptor which activates this enzyme. In the next illustration you will see that the qualitative effect of α_2-adrenoceptor activation is dictated by the function specificity of the adenylate cyclase activator. For example, when vasopressin is infused into the same kidney preparation as previously described, water and sodium retention occurs. There is considerable evidence that this hormone mediates its effect through activation of adenylate cyclase-cAMP beginning with the observations of Handler et al. (2). When epinephrine is used to activate the α_2-adrenoceptor as in the previous experiment, it reversed the effect of vasopressin (32c). Thus, in the one circumstance (furosemide $\rightarrow$ cAMP $\rightarrow$ sodium excretion) epinephrine caused sodium retention and in the other circumstance

(AVP-cAMP-water and sodium retention) epinephrine causes the opposite effect, the induction of sodium excretion. While this type of experiments permit us to conclude that the results are due to α_2-adrenoceptor activation, they do not establish the sites at which effects are occurring (ie. tubular versus vascular). Nevertheless, similar effects of α_2-adrenoceptor activation on AVP mediated events have been demonstrated in isolated perfused collecting ducts (33).

The above example of opposite effects of α_2-adrenoceptor activation depending on the receptor agonist used to activate adenylate cyclase focuses on one issue, the basis for specificity of α_2-adrenoceptor effect. However, such a peculiar basis for selectivity of effect raises certain questions. 1) Since α_2-adrenoceptors are present on most cell types in the body and only produce one effect - inhibition of adenylate cyclase - what is their physiologic role? 2) What determines their organ specificity of effects? 3) Is their activation dependent on locally released norepinephrine or epinephrine from the adrenal gland? 4) What is the relationship between α_2-adrenoceptor function and other receptors which mediate adenylate cyclase inhibition? 5) Are there pathophysiologic roles for α_2-adrenoceptors? Obviously, with the area being less than ten years of age we have only partial answers to most of these questions, some of which I will address herein. Interestingly, there are a number of substantive research programs here in our medical school addressing these and related problems, so you will be hearing much more about these receptors from other groups in the near future. One example is the studies of α_2-adrenoceptors by the gastro-enterology group.

4. *Intestinal α_2-adrenoceptors.*

α_2-Adrenoceptors are present in the ileum (34) and probably throughout the GI tract with the similarities between the gut and in the kidney in the regulation of sodium and water reabsorption. Can α_2-adrenoceptor activation cause sodium and water retention in the GI tract as in the kidney? Functioning tumors of the lung, pancreas and other organs can cause secretory diarrhea through secretion of vasoactive intestinal polypeptide (VIP) or VIP type hormones (35). Clonidine can reverse or control these diarrheas by activation of α_2-adrenoceptors (36). The doses of clonidine used in treating these diarrheas are similar or slightly higher than those used in treatment of high blood pressure suggesting similarities between the α_2-adrenoceptor in the brain whereby this agent lowers blood pressure and the receptor in the gut which enhances salt and water reabsorption. Whether clonidine can effect secretory diarrhea due to cholera (which is due to ADP-ribosylation of the G_s protein) is unknown.

Clonidine can induce net GI retention of salt and water in the absence of exaggerated stimulation of adenylate cyclase through activation of α_2-adrenoceptors (37-40). When clonidine 0.3mg is given to normal human volunteers the net retention of sodium and water is increased impressively as shown by Schiller et al. (41). These observations are consistent with either of two possible mechanisms. One is that "basal" cAMP is mediating a tonal effect on salt and water handling and α_2-adrenoceptor activation inhibits the basal adenylate cyclase activity and thereby inhibiting transport. Alternatively, α_2-adrenoceptors may be affecting smooth muscle tone or other GI function independently of cAMP. An example of a calcium-mediated effect can be seen in vascular smooth muscle in which at least part of α_2-adrenoceptor mediated effect is blocked by calcium channel blocking agents.

Alpha$_2$-agonists such as clonidine or lofexidine can inhibit diarrhea induced by castor oil, morphine withdrawal, prostaglandin E_2, serotonin and dibutyryl cAMP. Nakaki et al. (39) have argued that since the diarrheal effect of dibutyryl cAMP is also inhibited by clonidine that this α_2-agonist has effects independent of cAMP. The issue is made even more complex by the fact that a number of calcium channel (slow) blockers are also α_2-adrenoceptor blocking agents (see below). The issue of cAMP dependency of α_2-adrenoceptor mediated effect in smooth muscle tissues is not resolved and any studies of these α_2-adrenoceptor effects should include monitoring of cAMP formation or secretion if possible.

In our experience 20-30% of patients treated with clonidine for hypertension have side effects which are probably related to this α_2-adrenoceptor mediated effect on salt and water handling in the GI tract. These side effects are dryness of the mouth (and of the eyes) and constipation. Thus, these α_2-adrenoceptor-mediated effects are clinically relevant.

Narcotic agonists or opioid peptides also enhance salt and water reabsorption in the G-I tract and have many other effects similar to α_2-adrenoceptor agonists. They produce drowsiness, lowering of blood pressure, constipation, increased retention of salt and water in the small bowel and a withdrawal syndrome that can be at least partially controlled using clonidine, an α_2-adrenoceptor agonist. At the molecular level they can also activate specific cell membrane receptors that inhibit adenylate cyclase through a GTP binding protein in the GI tract and in the brain as does clonidine (41-46). Alpha$_2$-adrenoceptor agonists have been demonstrated to release β endorphins from brain tissue of SHR and could conceivably produce some of the similarities of effects of these two drug classes in vivo by this

mechanism (47). However, most of the evidence indicates that opioid peptides and α_2-adrenoceptor agonists mediate their effects directly through their respective receptors on cell membranes but possibly through a closely linked post-receptor mechanism. In fact, clonidine in addition to controlling opiate withdrawal symptoms (48,49) can also control the diarrheal symptoms of this syndrome (50).

Diabetic diarrhea is a syndrome that may be due to loss of adrenergic regulation of salt and water reabsorption in the small bowel due to defective release of catecholamines onto α_2-adrenoceptors. Chang et al. (51) have proposed use of α_2-adrenoceptor agonists such as clonidine for control of this syndrome.

Cyclic AMP induced water secretion appears to be localized in the crypt cells at the base of the villi in the large and small bowel (52-55). Thus, the α_2-adrenoceptor induced effects that are mediated by cAMP would be expected to occur at these sites.

5. *Vascular α-adrenoceptors.*

Both α_1- and α_2-adrenoceptors are present on vascular tissues and mediate increased tone in arterioles and veins. The predominant α-adrenoceptor mediating arteriolar constriction in most beds is of the α_1-type (56-68). Both types of α-adrenoceptors are present on veins and the predominance of one vs. the other is variable. The venous pooling and orthostatic hypotension that occurs with initiation of therapy in some patients with the α_1-blocker prazosin, indicates that this is a predominant venous receptor type in those patients. However, nearly all patients overcome this tendency to venous pooling of blood within 24 hours of continued therapy with prazosin, yet the α_1-adrenoceptors remain blocked.

Thus, α_2-adrenoceptors appear to assume the mediator role of norepinephrine-maintained venous tone in these patients. The molecular mechanism whereby α_2-receptors could be directed to do this is unknown.

Several years ago there was a flurry of interest in prazosin in the treatment of congestive heart failure (CHF). However, its predominant beneficial effects were apparently as temporary as the orthostatic hypotension occurring in some hypertensive patients. My suspicion is that the temporary blockade of sympathetic nervous system-mediated venous tone is the explanation for the "tolerance" that occurs to prazosin during treatment of congestive heart failure. Its use in treatment of CHF has now been largely abandoned unless patients simultaneously have hypertension and the individual patient can be demonstrated to have substantive beneficial effects of prazosin.

Angiotensin and mineralocorticoids potentiate α_2-adrenoceptor mediated vaso and/or venoconstriction (72-77). Thus, in vitro studies in which these hormones are absent may underestimate the potential for α_2-adrenoceptor effects. Angiotensin in renal vascular disease and/or glucocorticoids in Cushings syndrome could theoretically contribute by enhancing α_2-adrenoceptor mediated effect in these conditions. Also, some of the antihypertensive action of converting enzyme inhibitors appears to be due to reduction of α_2-adrenoceptor mediated vasoconstriction.

In the spontaneously hypertensive rat (SHR) model of essential hypertension α_2-adrenoceptors mediate an exaggerated vasoconstrictor response which has been suggested to be a contributing factor to elevated blood pressure (78). In fact, the supersensitivity to norepinephrine in the tail artery of the SHR is entirely α_2-adrenoceptor mediated and is associated with increased α_2-adrenoceptor density in this arteriolar bed (79). Exaggerated

vasoconstrictor responses are present in humans with essential hypertension and in most animal models of hypertension. However, these are not clearly α-adrenoceptor specific and the relative roles of α_2- versus α_1-receptor mediation of this supersensitivity has only been studied in the model mentioned above. We are particularly interested in this issue because of the earlier findings of high α_2-adrenoceptor density in kidneys of genetic models of rat hypertension (80,81).

There is another possible contributing mechanism to vasoconstrictor supersensitivity that is not specific for α-adrenoceptors (82). Prostaglandin synthesis occurs with vasoconstriction. Prostaglandins vasodilate and thereby modulate or limit vasoconstriction (83). PGE_2 (and PGI_2) stimulation of adenylate cyclase is defective in SHR and Dahl hypertensive rat renal membranes and in platelets of patients with essential hypertension (85-87). Such a defect in vascular tissue of patients with hypertension could contribute to non-specific vasoconstrictor supersensitivity.

Vascular α_2-adrenoceptors increase vascular tone by opening slow calcium channels thus permitting entrance of extracellular calcium resulting in contraction (88-91). Thus, many calcium channel blocking agents possess α_2-adrenoceptor blocking properties (88-91), a few having α_1-adrenoceptor blocking activity as well (88).

α_1-Adrenoceptor mediated vasoconstriction, on the other hand, is associated primarily with release of calcium from intracellular sites and is independent of/or less dependent on extracellular calcium for contraction (94).

While α-adrenoceptor activation can reduce vascular cAMP content (95), the quantitative role of inhibition of adenylate cyclase versus that mediated

by permitting Ca^{++} entry in α_2-adrenoceptor mediated vasoconstriction has not been established.

Vascular α_1-adrenoceptors may be concentrated in the vicinity of the synapse and α_2-adrenoceptors at extrasynaptic locations (69,97). Part of the basis for this conjecture is that Yamaguchi and Kopin found differential effectiveness of blocking agents in their capacities to inhibit vasoconstriction induced by nerve stimulation versus that which was induced by norepinephrine infusion. For additional evidence see review by Timmermans and van Zweiten (26).

6. *Cardiac α-adrenoceptors*.

The association of β-adrenoceptors, adenylate cyclase-cAMP and enhanced cardiac function has been known for many years (98). α-Adrenoceptor activation can increase contractility (99) and can also reduce cAMP (100). However, there are very few studies in which the relative contributions of α_1 and α_2-adrenoceptors to cardiac function or dysfunction have been determined. Even when the α_1-selective blocking agent prazosin is used experimentally, it is frequently in concentrations that are sufficiently high to block α_2-adrenoceptors. Another complicating factor is that when the first dose is given in vivo, it produces such pronounced systemic hemodynamic effects due to venous pooling that interpretation of direct cardiac effects are nearly impossible. Also, α_2-selective blocking agents have been rarely used to determine the relative physiologic or pathophysiologic roles of these receptors in cardiac dysfunction.

Clonidine depresses conduction and pacemaker activity (102). These studies were done prior to the awareness of post-synaptic location of α_2-adrenoceptors (9) so the authors concluded that presynaptic effects were

mediating the effects of clonidine. Rosen et al. (103) found that α-adrenoceptors decrease Purkinje fibre automaticity. While this event is probably α_2-adrenoceptor mediated, again the perspectives concerning selectivity were not published until after these studies were done.

Alpha-adrenergic receptors contribute to dysrhythmias during myocardial ischemia and reperfusion in animal models. Sheridan et al. (104) reduced ischemia-reperfusion PVC's in cats by more than 95% with phentolamine and >85% with prazosin and the morbidity from >20% to 1% by these α-adrenoceptor blocking agents. The selectivity of α_1- vs. α_2-blockade was not established in these studies, so whether these are α_2-adrenoceptor mediated contributions to arrhythmias is unknown.

There has been considerable interest in a possible mediator role of α-adrenoceptors in variant angina (105). Ergonovine, an agonist for several receptor types including α_2-adrenoceptors (106) precipitates coronary spasm in nearly all such patients and is used as a diagnostic tool in this syndrome. While coronary sinus norepinephrine concentration may be elevated in some patients, it is not consistently increased (107,108) and increased sympathetic outflow is not the mechanism for variant angina (109). If α-adrenoceptors mediate this remarkable problem, it is because of increased localized response or possibly platelet mediated events which might involve their α_2-adrenoceptors.

α_1-Adrenoceptors are not involved in the syndrome. It is not precipitated by the α_1-selective agonist phenylephrine nor is it blocked with prazosin (105). Chierchia et al. (105) found that the non-selective blocking agent phentolamine was ineffective in preventing angina in 5 of their patients. However, the infusion was terminated because of major hemodynamic effects. Consequently, their study is inconclusive in exclusion of

α_2-adrenoceptors in this syndrome. To my knowledge the definitive study in which an α_2-adrenoceptor selective blocker is properly administered has not yet been published. The fact that calcium channel blockers with α_2-specific blocking effects are so beneficial in this syndrome and that the α_2-adrenoceptor agonist Ergonovine reproducibly precipitates it suggests a localized exaggerated α_2-adrenoceptor response in the coronary arteries (or platelets) of these patients.

7. *Platelet α-adrenoceptors.*

All of the α-adrenoceptors on platelets are of the α_2-type. When activated, they inhibit adenylate cyclase and induce aggregation (110-114). Clonidine and other synthetic agonists are partial agonists of this α_2-adrenoceptor (112,115) as in the parotid gland (116). Platelet α_2-adrenoceptor density increases during menstruation (117) and has been reported to vary with age (117,118). Platelet α_2-adrenoceptor density changes reciprocally to plasma norepinephrine concentration and is probably directly regulated by circulating catecholamines (119,120). Platelet α_2-adrenoceptor density is increased and they are hyperaggregable in patients with anorexia nervosa (121). Their density is purportedly increased in spastic but not in obstructive Raynaud's syndrome (122).

Yokoyama (123) reported no enhancement of platelet α_2-adrenoceptor sensitivity in angina-free patients with myocardial infarction. However, in patients with variant angina the threshold epinephrine concentration required for initiating aggregation was shifted from 0.1 μMol in normals and those with infarctions to .012 μM in platelets from patients with variant angina (123). Thus, α_2-adrenoceptor supersensitivity may be involved in some way in

variant angina and is consistent with the previous arguments concerning ergonovine as a test substance in this syndrome.

Platelet α_2-adrenoceptor density and affinity appear to be normal in patients with essential hypertension (124). Interestingly, in normotensive WKY rats platelets do not have α_2-adrenoceptors and epinephrine does not induce platelet aggregation. However, in spontaneously hypertensive rats α_2-adrenoceptors are present and when activated they inhibit adenylate cyclase as in humans (125).

Platelet α_2-adrenoceptor density is markedly decreased along with the aggregating and serotonin release responses to epinephrine in some patients with "essential" thrombocythemia (126). This defect could thus contribute to abnormal bleeding in this disorder.

8. *α-Adrenoceptors and lipolysis.*

Adrenergic regulation of metabolism in fat cells is a particularly interesting and dynamic area with emphasis on α_2-adrenoceptors (127-133). The adrenoceptor linkages to membrane and intracellular events are very similar to the interrelationships of these regulatory units in other tissues α_2-Adrenoceptor activation can inhibit isoproterenol, GTP, and forskolin activated adenylate cyclase (and lipolysis). Pertussis toxin blocks this α_2-adrenoceptor mediated inhibition of lipolysis and enhances the lipolytic response in vivo suggesting a tonal role of receptor inhibition on the rate of lipolysis (128). Adenosine and prostaglandins (particularly in higher concentrations) can also inhibit lipolysis. There is some evidence that epinephrine is the physiological agonist for human fat cell α_2-adrenoceptors (131).

While there is some variability between species and body regions of fat cell α_2-adrenoceptors, there are some patterns that remain constant. One is that fat α_2-adrenoceptor density and responsiveness increases with age and with obesity (128-131). There are approximately 600,000 α_2-adrenoceptors on each human fat cell and the number increases with the size of the cell (131). Fasting changes the response in obese human fat cells to norepinephrine from stimulation to inhibition (133,134).

Kather (135) has found the balance of α_2-inhibition versus β-adrenergic stimulation of lipolysis is shifted in hyperthyroidism in favor of the lipolytic component. In hypothyroidism, diabetes mellitus or during prolonged starvation the α_2-adrenoceptor responsiveness is increased and may predominate over β-adrenoceptor stimulation. The underlying mechanisms whereby these ratios change are not yet established.

α_1-Adrenoceptors are also present on human adipocytes. Their activation increases phosphatidyl inositol turnover and Ca^{++} entry into the cell but have no effect on lipolysis (136). The second messenger between α_1-adrenoceptors and several other receptor types (not α_2) and Ca^{++} release is inositol triphosphate. (136b).

An increased level of α_2-adrenoceptor activity could be a causative factor in obesity (128). However, this is still rather speculative. A similar hypothesis was proposed by Prior (137) who suggested that prostaglandin overproduction might contribute to obesity.

9. *α-Adrenoceptors and insulin release.*

Activation of α_2-adrenoceptors in the islets of Langerhans results in inhibition of insulin release (138-142). Recent studies by Kato and Nakaki using dibutyryl cAMP have questioned the role of adenylate cyclase inhibition

in this effect of α_2-adrenoceptors and suggested that Ca^{++} may instead suppress insulin release (144). Whether α_2-adrenoceptors play a tonal role in regulation of insulin release is unknown. Excess activation of α-receptors in pheochromocytoma may contribute to lowered insulin and high blood sugar in this syndrome (145). Alpha-adrenoceptor blockade can control the high blood pressure and alteration of free fatty acid metabolism in pheochromocytoma (146).

Very frequently we see obesity, hypertension and diabetes mellitus or at least two of the three in the same patients. A simplistic hypothesis would be that exaggerated α_2-adrenoceptor-mediated effects contribute to these disease processes and that they could be alleviated by similar pharmacologic agents.

10. *Some central nervous system effects of α_2-adrenoceptor activation.*

Activation of α_2-adrenoceptors in the central nervous system can alter many functions. The α_2-adrenoceptors that mediate the antihypertensive effects of methyldopa and clonidine are located in the hypothalamus and medullary relay nuclei (31,32) and nucleus tractus solitarius (147).

The sensitivity of drowsiness to α_2-adrenoceptor agonists, as in GI retention of salt and water, is consistent with a tonal role of cAMP in maintenance of mood. When yohimbine, an α_2-selective antagonist used for centuries in Europe and Asia as an aphrodisiac and for depression, was given to normal volunteers, it produced increased sympathetic outflow and a shift in mood rating scales from calm toward excited states (148). Thus, α_2-adrenoceptors appear to have a tonic role in the brain of suppressing mood and blood pressure.

Activation of α_2-adrenoceptors in the locus coeruleus inhibits firing by hyperpolarizing cells (149) as occurs in peripheral sympathetic neuron terminals when the presynaptic α_2-adrenoceptor is activated (150). This α_2-adrenoceptor may thus operate through a Ca^{++} dependent mechanism to hyperpolarize locus coeruleus cells (149) as has been suggested for peripheral sympathetic neurons (151). However, there is evidence in the brain that these events are cAMP mediated (151b).

Clonidine and narcotics or opioid peptides produce very similar effects on intracellular recordings from locus coeruleus neurons, yet they act through distinct receptor mechanisms (152). However, α_2-agonists and opiates may hyperpolarize locus coeruleus neurons through a common mechanism since clonidine is effective in suppressing symptoms of opiate withdrawal by a functionally parallel action on central noradrenergic neurons (48,49,152). Because of the similarities noted previously between clonidine and opiate effects on salt and water reabsorption from the small bowel, the molecular mechanisms may again be similar.

α_2-Adrenoceptor activation increases the depth and duration of anesthesia (153). Alternatively, α_2-adrenoceptor blockade produces opposite effects (148), again supporting the contention that α_2-adrenoceptors play a role in wakefulness or drowsiness.

There have been very few investigations concerning α_2-adrenoceptor mediated events in the kidney even though these receptors constitute a large majority of renal α-adrenoceptors (80,81). α_1-Adrenoceptors mediate catecholamine induced renal vasoconstriction (56) and some of the sympathetic nerve mediated sodium retention (154). Under the circumstances described above α_2-adrenoceptors have been demonstrated to increase (32b) and to

decrease (32c) renal sodium retention depending on the function specific activation of adenylate cyclase.

11. *Renal α-adrenoceptors*.

α-Adrenoceptors have been reported to inhibit (155,156) and to stimulate (157) renin release. While the definitive experiments have not yet been done, we suspect that the α-adrenoceptor inhibitory to renin release is of the α_2-type. Some of the differences may be due to: 1) Differences in presence or absence of adenylate cyclase activation in models used; for example, if the renin releasing adenylate cyclase is not stimulated the α_2-adrenoceptor would not be expected to inhibit renin release. Alternatively, α_2-adrenoceptor mediated vasoconstriction through an ischemic mechanism would be expected to stimulate rather than inhibit renin release. 2) Inappropriate experimental design, particularly in the relationships between the mechanism for activating the adenylate cyclase mediating renin release and choice and dose of specific blocking agents. With new technologies and perspectives described above, we are now aggressively pursuing this issue in our laboratory.

12. *The presynaptic α_2-adrenoceptor*.

α_2-Adrenoceptors are present on peripheral sympathetic nerve terminals and, when activated, can inhibit depolarization-induced norepinephrine release. Even though these receptors are widespread, there is considerable debate concerning their physiologic importance (for review see 158).

13. *Miscellaneous.*

Other α_2-adrenoceptor mediated events include lowering of body temperature (159), suppression of growth hormone release (159b) ($?\alpha_2$), inhibition of mediator release from mast cells (160), and from platelets (160,162). They affect transmission of pain in the spinal cord (163) and have been reported to restore transmission through injured spinal cord (164). They are present in bronchi (165) and reported to be increased in experimental asthma (166). They are present in the uterus and change with estrogen administration. Thus, they may be involved in myometrial contraction (167).

Somatostatin inhibits adenylate cyclase in many tissues resulting in reversal of cAMP mediated effects (168) including the intermediate lobe of the pituitary gland (169). The effects of adenosine on adenylate cyclase are nearly as complicated as the β- and α-adrenergic systems and are not as well described at this time. However, there is considerable interest in pharmaceutical development in this area (170).

14. *Abnormalities in hypertension.*

We have recently found receptor specific defectives in adenylate cyclase activation that are associated with excess renal α_2-adrenoceptors in rat models of human hypertension (170,171). The renal adenylate cyclase response to prostaglandin E_2 and I_2 and to parathyroid hormone is reduced in both hypertensive strains of rat. We suspect that these defective responses have biological significance because both hypertensive strains have renal leaks of calcium, decreased serum calcium and elevated PTH (171,172) as noted by McCarron et al. in patients with essential hypertension (174-176).

Kestleloot's findings in hypertensive patients, incidentally, contrast with McCarrons's (177).

Schedl et al. (178) very recently reported abnormalities of serum Ca and PTH in the spontaneously hypertensive rat that are related to defective response in the small bowel to Vitamin D (169). Calcium absorption by the duodenum and ileum is markedly reduced and sodium absorption is increased (in the duodenum only) in the SHR. While the 1,25-dihydroxycholecalciferol [1,25-$(OH_2)D_3$] was the same in the WKY and SHR, the 25-hydroxycholecalciferol was increased. Thus, Schedl et al. conclude 1) 1,25-$(OH_2)D_3$ is inappropriately low relative to the high PTH and depressed calcium absorption and 2) the depressed calcium absorption with normal 1,25-$(OH_2)D_3$ shows a defective gut responsiveness to Vitamin D and may explain low serum ionized calcium in the SHR.

We suggest that the defective adenylate cyclase response to PTH that we have demonstrated in renal membranes is not organ specific and that the findings of Schedl et al. are consistent with a similar biochemical defect regulating calcium (and possibly sodium) handling in the small bowel.

While this defective adenylate cyclase response to PTH is the probable explanation for the altered calcium metabolism, it may be an epiphenomenon relative to hypertension. We find the defective response to the vasodilatory-natriuretic prostaglandins more attractive as an explanation for exaggerated renal retention of sodium and increased vascular resistance to these animal models and to humans with essential hypertension.

In summary, pre- and postsynaptic effects at sympathetic neuron terminals of the α-adrenoceptors and their capacity to inhibit adenylate cyclase has been known for many years. However, clarification by

pharmacologic descriptions of the α_1- and α_2-adrenoceptor and identification of the α_2 as the one inhibitory to adenylate cyclase occurred only seven years ago. While tremendous progress has evolved during the last seven years, there are many unanswered questions, some of which are noted in the text above.

We feel that there is great potential in pathophysiologic roles for α_2-adrenoceptors and in pharmacologic alteration thereof.

I hope that this overview will be of some help to my clinical colleagues in providing perspectives of currently useful agents such as calcium channel blocking agents, clonidine, methyldopa and some of their effects described above. Perhaps it will be of some use in facilitiating much better experimental design involving α-adrenoceptor studies by my research colleagues at both the basic and clinical levels. If so, the time and effort required to develop this review will have been worthwhile.

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