British Journal of Anaesthesia 1993; **71**: 108–118

ALPHA$_2$ ADRENOCEPTOR AGONISTS AND ANAESTHESIA

Y. HAYASHI AND M. MAZE

The clinical application of alpha$_2$ adrenergic agonists for anaesthesia has no precedent in our discipline. New classes of anaesthetic drugs, or even new members of an existing class, are usually promoted by an immense pharmaceutical industry effort. The alpha$_2$ adrenergic agonists have arrived on the scene with no hyperbole: these drugs will succeed (or fail) on their own merits. In addition, more is known about the underlying mechanism of action of these compounds than is known about all other anaesthetic agents. In this review we have concentrated on basic, applied and clinical pharmacology of these agents as they relate to anaesthesia.

BASIC PHARMACOLOGY

Classification of adrenergic receptors

Until recently, the framework for the understanding of adrenergic responses was based on the dual receptor theory of Ahlquist [5]. He differentiated adrenergic receptors into alpha and beta based on the rank order of potency of various natural and synthetic catecholamines in different physiological preparations. Ahlquist concluded that there was no clear correlation between excitatory or inhibitory actions of catecholamines and a particular receptor type. Activation of either alpha or beta adrenergic receptors produced excitatory effects in some tissues and inhibitory effects in others. Subsequently Lands and colleagues [86] showed that the rank order of potency of a series of catecholamines for a variety of beta adrenergic receptor-mediated responses could be used to identify two types of beta adrenergic receptors, beta$_1$ and beta$_2$. Both the beta$_1$ and the beta$_2$ adrenoceptors stimulate the membrane-bound enzyme adenylate cyclase, leading to the intracellular accumulation of cyclic adenosine 3′, 5′-monophosphate (cAMP), a ubiquitous second messenger present in virtually all cells and tissues [140]. The beta adrenoceptors have become model systems for investigators studying the structure and function of hormone and drug receptors in cell membranes because of their ubiquity, close coupling to a biochemical effector unit and the widespread clinical application of ligands acting at these receptors [42, 88, 137].

In the alpha adrenoceptor field, the next major advance was based on the identification of a receptor which regulated the release of neurotransmitters [108]: from this it was inferred that the receptor was located at a presynaptic site [87]. This led to a subdivision of alpha adrenoceptors, based on their synaptic location, into postsynaptic alpha$_1$ and presynaptic alpha$_2$ [14]. A classification based strictly on anatomic location has proven to be untenable in the light of postsynaptically and even extrasynaptically located alpha$_2$ adrenergic receptors not linked to neurotransmitter release [44]. As more selective alpha adrenoceptor antagonists became available, it was possible to definitively separate the alpha adrenoceptors into two subtypes on a pharmacological basis [24]. The current pharmacological classification of alpha$_2$ *vs* alpha$_1$ is based on the antagonists yohimbine and prazosin. At alpha$_1$ receptors, prazosin is more potent than yohimbine, whereas at alpha$_2$ receptors, yohimbine is more potent than prazosin.

Structure of the alpha$_2$ adrenoceptor

The structure of the alpha$_2$ adrenoceptor is similar to a host of other neurotransmitter receptors, including other adrenergic (alpha$_1$, beta), muscarinic, dopamine, opioid, adenosine and serotonin receptors. Each of these receptor proteins is comprised of a single polypeptide chain which weaves back and forth through the cell membrane. The hydrophobic intramembranous portions of each of the adrenergic receptors are similar in their primary structure. From this, one may deduce that these hydrophobic portions are probably the site which recognizes noradrenaline, the ubiquitous neurotransmitter for each of the adrenergic receptors. However, on the cytoplasmic side, the adrenergic receptor proteins exhibit considerable differences in structure. The characteristic adrenergic responses are predicated by these structural features, especially in the manner in which they provide "contact points" for the host of guanine nucleotide binding proteins (G proteins).

Classification of alpha$_2$ adrenergic receptors

Two separate nomenclatures, based on either pharmacological (alpha$_{2A}$, alpha$_{2B}$ or alpha$_{2C}$) or

(Br. J. Anaesth. 1993; **71**: 108–118)

KEY WORDS

General anaesthesia. Pharmacology. clonidine, dexmedetomidine. Receptors: adrenergic.

YUKIO HAYASHI*, M.D., Department of Anesthesia, Stanford University, Stanford, CA 94305 U.S.A. MERVYN MAZE, M.B., CH.B., M.R.C.P., Anesthesiology Service (112A) Veterans Affairs Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304, U.S.A.

*Present address: Department of Anesthesiology, National Cardiovascular Center, Osaka 565, Japan.

Correspondence to M. M.

molecular biological probes [23] agree to the existence of at least three different alpha$_2$ isoreceptors. According to the molecular biological classification, these are defined by the chromosomal location of the gene for the receptor, being either alpha$_{2C2}$, alpha$_{2C4}$ or alpha$_{2C10}$. Different brain regions, like most other tissues in the body, are usually populated by more than one isoreceptor.

G proteins

These "coupling proteins" promote transmembrane signalling to a discrete effector mechanism which may be a transmembrane ion channel or an intracellular second messenger cascade [29]. There are more than 20 species of G proteins which are characterized by differences in the amino acid sequence of one (alpha) of the three subunits. These discrete differences in the alpha subunit provide the unique response mediated by each of the adrenergic receptors. At least four different G proteins couple to the alpha$_2$ adrenoceptors, including G_{i1-3} and G_o.

Effector mechanisms

A feature common to all alpha$_2$ adrenergic receptors is their ability, when activated, to inhibit adenylate cyclase. The resulting decrease in the accumulation of cAMP attenuates the stimulation of cAMP-dependent protein kinase and hence the phosphorylation of target regulatory proteins. However, in many cases a decrease in cAMP production is not sufficient to mediate the effects of the alpha$_2$ adrenoceptor. Efflux of K^+ through an activated channel can hyperpolarize the excitable membrane and provide an effective means of suppressing neuronal firing. Alpha$_2$ adrenoceptor stimulation also suppresses Ca^{2+} entry into the nerve terminals which may be responsible for its inhibitory effect on secretion of neurotransmitters.

APPLIED PHARMACOLOGY

Alpha$_2$ adrenergic agonists

These can be grouped into three main classes: phenylethylamines (e.g. amethylnoradrenaline), the imidazolines (e.g. clonidine) and oxaloazepines (e.g. azepexole).

Clonidine, an imidazole compound, is a selective agonist for alpha$_2$ adrenoceptors with a ratio of 200 : 1 (alpha$_2$:alpha$_1$). In many models of alpha$_2$ action, clonidine has been identified as a partial agonist. Clonidine is rapidly and almost completely absorbed after oral administration and reaches peak plasma concentrations within 60–90 min by this route. Clonidine may also be delivered via a time release transdermal patch, although a minimum of 2 days must elapse before a therapeutic concentration is achieved [144]. The elimination half-life of clonidine is between 9 and 12 h, and approximately 50 % of the drug is metabolized in the liver to inactive metabolites while the rest is excreted unchanged by the kidney.

Methyldopa is metabolized to methylnoradrenaline which is a full agonist at the alpha$_2$ receptor and has 10-fold selectivity for the alpha$_2$ over the alpha$_1$ adrenoceptor. Because transformation into the active compound is necessary, effects are slow to develop (4–6 h) and somewhat unpredictable. It is the only parenteral preparation available for clinical use in the U.S.A. Guanabenz is similar to clonidine in its effects: however, it is less potent and shorter acting with a terminal elimination half-life of 6 h. Guanfacine has the longest half-life (14–18 h) of all the clinically available alpha$_2$ agonists. Both the latter two drugs are guanidine compounds.

Medetomidine (4(5)-[1,2,3-dimethylphenylethyl]-imidazole) is the prototype of the novel super-selective alpha$_2$ agonists. It is an order of magnitude more selective than clonidine and is a full agonist at this class of receptor [129]. Medetomidine is extremely potent and is active at small nanomolar concentrations and has been widely used in veterinary practice in Europe. Since the D-enantiomer of this racemate is the active ingredient, dexmedetomidine has been developed for clinical use. Phase II studies with this compound have been launched in the U.S., while in Europe the drug is in phase III clinical trials.

Some ligands have an imidazole ring which enables them to bind to non-adrenergic imidazole-preferring receptors, as well as to the alpha$_2$ adrenoceptor [51]. The cardiovascular properties of alpha$_2$ ligands vary considerably, depending on whether or not the imidazole-preferring receptor is also bound [142].

CLINICAL APPLICATION OF ALPHA$_2$ AGONISTS

Pharmacological responses of alpha$_2$ agonists on different systems

Central nervous system. Sedation is one of the most consistent effects mediated by central alpha$_2$ receptors [43]. While this property is an undesirable side effect when clonidine is administered to patients with hypertension, it has been used to great advantage as premedication in anaesthesia. This sedative effect of alpha$_2$ agonists is potentiated significantly when they are administered together with a benzodiazepine [126]. Recently, the locus coeruleus was shown to be a principal region responsible for the sedative effect [35, 127].

Another characteristic effect of alpha$_2$ agonists in clinical situations is anxiolysis, which is comparable to that produced by benzodiazepines [26, 54, 153]. Clonidine may also depress panic disorder in humans [147]. However, larger doses of alpha$_2$ agonists may produce anxiogenic responses through non-selective activation of alpha$_1$ receptors [133].

Alpha$_2$ adrenergic receptor activation produces a potent analgesic response, involving both supraspinal and spinal sites [110, 151, 154]. In animal experiments, clonidine exerts a more potent analgesic effect than morphine [55]. Furthermore, its potency is enhanced synergistically with concomitant treatment with opioids [103, 105, 134, 152]. Alpha$_2$ agonists and opioids mediate the analgesic action through independent receptors, although these two classes of agents have a similar transduction pathway in their effector mechanism [22]. This may be the mechanism for the development of cross-tolerance between these two agents [107, 136]. Alpha$_2$ agonists

suppress the undesirable physiological and psychological symptoms after withdrawal of opioids [62]. Recently, the usefulness of alpha$_2$ agonists has been extended to other withdrawal states, such as alcohol and benzodiazepines [10, 36, 155]. In humans, dexmedetomidine was reported to suppress ischaemic pain [76] and to attenuate the affective component of ischaemic pain [82]; yet, i.v. dexmedetomidine, in the dose range 25–50 μg kg^{-1}, did not affect the experimental pain threshold [76].

The most impressive action of alpha$_2$ agonists in the central nervous system is the ability to reduce anaesthetic requirements. Kaukinen and Pyykko [81] demonstrated a modest reduction (15%) of MAC of halothane after subacute administration of clonidine in rabbits. Bloor and Flack [16] observed that acutely administered clonidine reduced MAC of halothane by up to 50% in a dose-dependent fashion. This effect was antagonized by tolazoline, an alpha$_2$ antagonist. There is a ceiling to the reduction of MAC effect of clonidine because of its ability to stimulate alpha$_1$ adrenoceptors. More selective alpha$_2$ agonists reduce the MAC of volatile anaesthetics to a much greater extent. Azepexole was shown to reduce MAC of isoflurane by 85% in dogs [94], while dexmedetomidine decreased MAC of halothane by more than 95% in animals [132, 149], indicating that it may be an anaesthetic in its own right. This reduction in anaesthetic requirement may also be demonstrated in humans and is not limited to volatile anaesthetics (see below).

Intraocular pressure can be reduced by alpha$_2$ agonists and these agonists may also attenuate the increase in intraocular pressure associated with laryngoscopy and tracheal intubation [60, 75, 85]. Although an early report showed that the action may be a result of reduction in production and augmentation in outflow of aqueous humour [83], this has yet to be established. The imidazoline preferring receptor has also been implicated in this action [113].

Experimental application of alpha$_2$ agonists and antagonists in the study of neuroprotection from cerebral ischaemia has resulted in conflicting data. Hoffman and colleagues [71, 72] reported that the alpha$_2$ agonists clonidine and dexmedetomidine improve outcome from incomplete global ischaemia. On the other hand, Gustafson and colleagues [65, 66] demonstrated that idazoxan, an alpha$_2$ antagonist, could also protect against global ischaemia. This apparent paradox may be reconciled by a recent report [92] that both idazoxan and rilmenidine (alpha$_2$ antagonist and agonist with affinity for the imidazole-preferring receptor) can exert a protective effect against cerebral ischaemia. The authors hypothesized that the imidazole-preferring receptor, and not alpha$_2$ receptors, are involved in the neuroprotective mechanism.

Cardiovascular system. The action of alpha$_2$ agonists on the cardiovascular system may be classified as peripheral or central. Alpha$_2$ agonists inhibit noradrenaline release from peripheral prejunctional nerve endings and this property, in part, contributes to the bradycardiac effect of alpha$_2$ agonists [37]. At present, there is no evidence to support the existence of postsynaptic alpha$_2$ receptors in the myocardium [45, 74]; therefore, direct effects of alpha$_2$ agonists on the heart are doubtful. Postjunctional alpha$_2$ receptors are present in both arterial and venous vasculature where they produce vasoconstriction [125]. Among the different vascular beds, the effect of alpha$_2$ agonists on the coronary circulation is important. A putative vasoconstrictive action of alpha$_2$ agonists on the coronary vasculature would not be favourable in the ischaemic heart [31, 97]: however, these agonists can ameliorate any direct constriction by reducing sympathetic outflow [70]. Furthermore, alpha$_2$ agonists have been documented to release endothelial derived relaxant factor in coronary arteries [32] and to enhance coronary blood flow induced by endogenous and exogenous adenosine in an *in vivo* model [73]. Thus the effect on coronary arteries may be too complicated to distinguish clear changes in coronary blood flow in an *in vivo* model [130].

Central mediated hypotensive and bradycardiac effects of clonidine have been well recognized. The mechanism for these actions may involve inhibition of sympathetic outflow and the potentiation of parasympathetic nervous activity. However, the precise mechanism involved in these actions is not well understood. While the nucleus tractus solitarius (a site known to modulate autonomic control, including vagal activity) is an important central site for the action of alpha$_2$ agonists [84], other nuclei, including the locus coeruleus [141], the dorsal motor nucleus of vagus [122, 148] and the nucleus reticularis lateralis [50, 143] may also mediate hypotension, bradycardia, or both. It has been documented [20, 21, 142] that imidazole-preferring receptors play an important role in the hypotensive effect of alpha$_2$ agonists.

Alpha$_2$ agonists also have anti-arrhythmic properties. For example, dexmedetomidine prevents adrenaline-induced arrhythmias during halothane anaesthesia [68]. Not only central alpha$_2$ receptors, but imidazole-preferring receptors are involved [69]. The anti-arrhythmic effect is abolished in vagotomized animals [78].

The effect of alpha$_2$ agonists on the cerebral circulation during anaesthesia has been studied. Zornow and colleagues [156] and Karlsson and colleagues [80] demonstrated that dexmedetomidine decreases cerebral blood flow in dogs anaesthetized with isoflurane and halothane. This characteristic may be favourable in protecting the brain from an abrupt increase in blood flow. This idea has been supported by a recent report by McPherson and Traystman [91], who showed that dexmedetomidine blunts the cerebrovascular response to hypoxic hypoxia during isoflurane anaesthesia.

Respiratory system. The respiratory depressant effects of clonidine are not remarkable unless massive doses are given [8, 102]. Eisenach reported that i.v. clonidine induces an hypoxic effect in ungulates and concluded that aggregation of platelets is responsible for this mechanism in this animal species [47]. Although alpha$_2$ agonists may cause mild respiratory depression [98], the effect of clonidine is less than that of opioid narcotics [58]. In clinically appropriate doses, respiratory depression may not be detected

TABLE I. *Preanaesthetic application of alpha$_2$ adrenergic agonists*

Drug	Route (dose)	Effect	Reference
Clonidine	Oral (300 μg)	Sedation Reduction in anxiety Decreased methohexitone	[153]
Clonidine	Oral (200 μg)	Reduction in anxiety Postoperative analgesia	[26, 28]
Clonidine	Oral (300 μg)	Sedation Reduction in anxiety Reduction in intraocular pressure	[85]
Clonidine	Oral (5 μg kg^{-1})	Decreased fentanyl by 45% Decreased haemodynamic response to intubation	[61]
Clonidine	Oral (200–300 μg) +n.g. (200–300 μg)	Decreased sufentanil by 40% Haemodynamic stability Decreased catecholamines	[57]
Clonidine	Oral (5 μg kg^{-1})	Decreased droperidol	[49]
Clonidine	Oral (225–375 μg)	Decreased thiopentone by 20%	[104]
Clonidine	Oral (600 μg)	Decreased propofol	[121]
Clonidine	Oral (150 μg)	Prolonged tetracaine spinal anaesthesia	[106]
Clonidine	Oral (5 μg kg^{-1})	Reduction in intraocular pressure Decreased haemodynamic response to intubation Decreased isoflurane by 30% Decreased fentanyl by 60–75% Haemodynamic stability	[60]
Clonidine	Oral (5 μg kg^{-1})	Decreased haemodynamic response to intubation Decreased isoflurane by 40% Decreased fentanyl by 75% Haemodynamic stability	[59]
Clonidine	Oral (4.7 μg kg^{-1})	Decreased catecholamines Haemodynamic stability	[115]
Dexmedetomidine	I.v. (0.6 μg kg^{-1})	Decreased isoflurane by 25% Decreased haemodynamic response to intubation	[7]
Dexmedetomidine	I.m. (1.0 μg kg^{-1})	Decreased thiopentone by 17% Decreased catecholamines	[1]

except with hypercapnic respiratory response studies [109]. There is no potentiation by clonidine of opioid-induced respiratory depression [11, 77]. In addition, nebulized clonidine attenuated bronchoconstriction in asthmatic patients [89].

Endocrine system. Alpha$_2$ agonists potentiate the secretion of growth hormone [64]. Although a precise mechanism for this action has not been elucidated, Deveasa and colleagues [40, 41] suggested that alpha$_2$ receptor activation is coupled to growth hormone releasing factor. Alpha$_2$ agonists which possess an imidazole ring in their structure may produce inhibition of steroidogenesis. However, at clinical doses, this effect is not likely to have serious consequences [95]. Alpha$_2$ agonists decrease sympathoadrenal outflow and these agents may suppress the stress response after surgical stimulation [87]. While *in vitro* studies indicate that alpha$_2$ agonists regulate catecholamine secretion in the adrenal medulla [67, 150], this effect has been questioned by others [114, 120]. The alpha$_2$ agonists also inhibit the release of insulin from the pancreatic beta cells directly [9]; again, this effect is not troublesome in clinical situations [93].

Gastrointestinal system. Decreased salivary flow is one of the advantages of the use of alpha$_2$ agonists as premedication [79]. Alpha$_2$ agonists may modulate release of gastric acid via a presynaptic mechanism [14]; yet no significant change in gastric pH is observed in humans [104]. The alpha$_2$ agonists may also prevent intestinal ion and water secretion in the large bowel, indicating an effective treatment for watery diarrhoea [90].

Renal system. Alpha$_2$ agonists induce diuresis. Inhibition of release of antidiuretic hormone (ADH) [111], antagonism of the renal tubular action of ADH [135] and increase in the glomerular filtration rate [138] have each been implicated in this mechanism. Recently, alpha$_2$ agonist-induced release of atrial natriuretic factor has also been suggested to contribute to the diuretic mechanism of alpha$_2$ agonists [30].

Haematological system. Aggregation of platelets is induced by alpha$_2$ agonists [124]. In the clinical setting, this is largely offset by the decrease in circulating catecholamines.

Use of alpha$_2$ agonists in anaesthetic practice

Preanaesthetic administration (table I). Since sedation and anxiolysis are necessary attributes of premedication, administration of alpha$_2$ agonists suits this purpose well [1, 6, 7, 28, 85, 153]. Another benefit of alpha$_2$ agonists as premedication are their ability to potentiate the anaesthetic action of other agents and to reduce anaesthetic requirements during surgery. This effect is observed universally, regardless of the type of anaesthetic, i.v., volatile or regional block. For example, Ghingnone and colleagues [61] reported that premedication with oral clonidine 5 μg kg^{-1}, reduced fentanyl requirements for induction and intubation by 45% in patients undergoing aortocoronary bypass surgery. In a similar patient population, Flack and colleagues [57] demonstrated that clonidine reduced sufentanil requirement by 40%. Engelman and co-workers [49] showed that preoperative clonidine 5 μg kg^{-1} decreased the dose

TABLE II. *Perioperative application of alpha$_2$ adrenergic agonists*

Drug	Route (dose)	Effect	Reference
Clonidine	Transdermal patch	Decreased isoflurane Haemodynamic stability Postoperative analgesia	[131]
Clonidine	I.v. (7 μg kg^{-1})	Postoperative decreases in catecholamines and vasopressin Haemodynamic stability Less postoperative shivering	[116]
Clonidine	I.v. (4 μg kg^{-1} + 2 μg kg^{-1} h^{-1})	Potentiation of morphine analgesia	[38]
Clonidine	Intrathecal (150 μg)	Prolonged bupivacaine spinal anaesthesia	[118]
Clonidine	Intrathecal (75, 150 μg)	Prolonged tetracaine spinal anaesthesia	[19]
Clonidine	Extradural (150 μg)	Potentiated lignocaine extradural anaesthesia	[146]
Clonidine	Extradural (90, 180 μg)	Sedation Haemodynamic stability	[99]
Clonidine	I.v. (5 μg kg^{-1})	Decreased oxygen consumption	[117]

of droperidol necessary to maintain haemodynamic stability in aortic surgery patients. Doses of thiopentone and propofol required for induction are also reported to be reduced by preanaesthetic treatment by clonidine and dexmedetomidine [1, 3, 4, 104, 121]. This characteristic may facilitate more rapid emergence from anaesthesia. In addition, oral clonidine 150 μg may prolong tetracaine spinal anaesthesia [106].

Alpha$_2$ agonists have been known to attenuate stress-induced sympathoadrenal responses. Minimizing haemodynamic changes after tracheal intubation and the noxious stimuli from surgery is an important goal for the anaesthetic care of the surgical patient. Carabine, Wright and Moore [28] suggested that clonidine 200 μg was a suitable dose and that larger doses did not offer any further advantage. Others have recommended larger doses of clonidine [60, 85, 153]. The efficacy of dexmedetomidine has been studied extensively in Finland. I.v. administration of the drug, in doses ranging from 0.3 to 0.6 μg kg^{-1}, provided optimal premedication effects [3, 4, 7, 75, 128]. Aantaa and co-workers [1, 2] studied i.m. dexmedetomidine, a clinically more appropriate route of administration, and showed that a dose of 1.0 μg kg^{-1} was adequate. However, the sedative effects may outlast the surgery at these doses. Flacke and colleagues [57] reported that the haemodynamic variables in patients undergoing aortocoronary bypass surgery were more favourable despite the fact that smaller doses of narcotics were used. Ghingnone and co-workers [61] corroborated these findings in a similar patient population. While these features also applied to patients undergoing aortic surgery [49, 115], this favourable property was absent in patients undergoing carotid artery surgery [112]. The successful application of alpha$_2$ agonists to geriatric patients is established [60, 85], but this therapy has not been extended to a paediatric population.

Addressing possible disadvantages of alpha$_2$ agonists as premedication, oral clonidine 300 μg did not affect tidal volume, ventilatory frequency or end-tidal carbon dioxide tension, but did attenuate the ventilatory response to carbon dioxide, suggesting that clonidine has a potential respiratory depressant effect [12]. On the other hand, Bailey and colleagues [11] demonstrated that oral clonidine 4–5 μg kg^{-1} did not depress the response to carbon dioxide. Similar findings have been reported by Jarvis and co-workers also [77]. Furthermore, these two reports demonstrated that oral clonidine did not potentiate respiratory depression exerted by opioids. Another common risk with the use of alpha$_2$ agonists is excessive cardiovascular depression, namely bradycardia and hypotension. These complications were described in several reports [1, 2, 28]. Atropine is the treatment of choice for bradycardia, but it should be noted that large doses of oral clonidine, 5 μg kg^{-1}, attenuate the effect of atropine [100]. On the other hand, clonidine potentiates the pressor effect exerted by ephedrine [101].

Intraoperative administration (table II). Although alpha$_2$ agonists have potent analgesic and sedative effects, these agents have not been used during operation in lieu of the usual anaesthetic agents. Thus far, there are only a few reports describing intraoperative administration of alpha$_2$ agonists. Segal and co-workers [131] examined the efficacy of systemic clonidine. They reported that the combination of oral and transdermal clonidine (which maintained the plasma concentration of clonidine at therapeutic concentrations) provided smaller anaesthetic requirements, greater haemodynamic stability, more rapid recovery from anaesthesia and less postoperative requirement for supplementary morphine for pain control in patients undergoing lower abdominal surgery. Quintin and colleagues [116] reported that in patients undergoing abdominal aortic grafting, perioperative infusion of clonidine 7 μg kg^{-1} over 120 min after aortic declamping, reduced noradrenaline, adrenaline and vasopressin concentrations during the recovery period. They concluded that although there was greater haemodynamic stability, larger fluid volumes were required during the postoperative period. Also, intraoperative clonidine infusion (a loading dose of 4 μg kg^{-1} following 2 μg kg^{-1} h^{-1} until closure of the peritoneum) may enhance the quality of postoperative analgesia by morphine [38]. A significant reduction in postoperative shivering episodes by clonidine treatment is also a consequence of this regimen.

Alpha$_2$ agonists may also be administered by the intrathecal or extradural route to potentiate local anaesthetic agents. Racle and colleagues [118] showed that intrathecal clonidine 150 μg prolonged

TABLE III. *Postoperative application of alpha$_2$ adrenergic agonists*

Drug	Route (dose)	Effect	Reference
Clonidine	Extradural (2 μg kg^{-1})	Postoperative analgesia	[17]
Clonidine	Extradural (150 μg)	Postoperative analgesia	[53]
Clonidine	Extradural (100–900 μg)	Postoperative analgesia Haemodynamic depression Sedation	[46]
Clonidine	Extradural (400 μg + 20 μg h^{-1})	Less postoperative morphine Sedation Prolonged local anaesthetics	[96]
Clonidine	Extradural (150 μg + 50 μg h^{-1})	Postoperative analgesia	[27]
Clonidine	Extradural (150 μg)	Prolonged extradural fentanyl	[123]
Clonidine	Extradural (150 μg)	Prolonged extradural bupivacaine	[25]
Clonidine	Extradural (150 μg)	Potentiated extradural morphine	[27]
Clonidine	Intrathecal (150 μg)	Postoperative analgesia	[56]
Clonidine	I.m. (2 μg kg^{-1})	Postoperative analgesia	[17]
Clonidine	I.v. (150 μg)	Postoperative analgesia	[145]
Clonidine	I.v. (5 μg kg^{-1} + 0.3 μg kg^{-1} h^{-1})	Postoperative analgesia Haemodynamic depression	[13]
Clonidine	I.v. (2 μg kg^{-1})	Decreased oxygen consumption	[39]
Dexmedetomidine	I.v. (0.2, 0.4 μg kg^{-1})	Less postoperative morphine Less postoperative shivering Sedation Haemodynamic depression	[6]

bupivacaine spinal anaesthesia in elderly patients undergoing hip surgery and this technique was superior to the addition of adrenaline 200 μg to bupivacaine. Bonnet and co-workers [19] demonstrated that clonidine prolonged tetracaine spinal anaesthesia dose-dependently. Concerning extradural anaesthesia, addition of clonidine to extradural lignocaine was reported to increase its anaesthetic potency. Another advantage of extradural clonidine during surgery is the provision of sedation and relative haemodynamic stability compared with plain lignocaine or lignocaine with adrenaline [99].

Postoperative administration (table III). The potent analgesic properties of alpha$_2$ agonists provide improved pain control in postoperative patients. Extradural administration is the most common route and has been investigated thoroughly. The efficacy of clonidine after operation depends on the dose and the severity of postoperative pain. In an early clinical study, Gordh [63] failed to demonstrate a significant analgesic effect of extradural clonidine 3 μg kg^{-1} in patients after thoracotomy. However, Bonnet and colleagues [18] observed that extradural clonidine 2 μg kg^{-1} produced brief but significant pain relief after peripheral orthopaediatric surgery. Recently, van Essen and co-workers [53] reported that extradural clonidine 150 μg produced postoperative analgesia in patients undergoing abdominal hysterectomy. On the other hand, Eisenach, Lysak and Viscomi [46] examined the analgesic effect of extradural clonidine 100–900 μg in 100-μg increments, in patients after total knee arthroplasty or abdominal surgery. Analgesia was estimated by verbal pain score and the need for supplementary i.v. morphine. Clonidine produced analgesia in a dose-dependent manner, achieving complete pain relief for up to 5 h without sensory or motor block at the largest dose (700–900 μg). However, larger doses were associated with disadvantages, including hypotension, bradycardia and transient sedation. Penon, Ecoffey and Cohen [109] reported that extradural clonidine 300 μg decreased the slope of the ventilatory response to carbon dioxide without changing end-tidal carbon dioxide, ventilatory frequency or minute ventilation. To reduce the side effects without affecting the analgesic property, continuous extradural administration after bolus injection of clonidine (800 μg bolus followed by 20 μg h^{-1}) is advocated as an alternative method [96]. With this continuous treatment, more than 6 h of analgesia was seen after Caesarean section. In comparison with single dose clonidine administration, several reports describe the effectiveness of combining extradural administration of clonidine with local anaesthetics or opioids. Adding 150 μg of clonidine to extradural fentanyl, morphine and bupivacaine resulted in longer duration of postoperative analgesia [25, 27, 123]. Furthermore, these combinations may reduce the effective dose of clonidine, resulting in less side effects. In addition, a recent report described the efficacy of intrathecal clonidine 150 μg as the sole analgesic agent after Caesarean section without remarkable side effects [56].

Systemic adminstration of clonidine for postoperative analgesia has also been reported. Bonnet and colleagues [17] compared the analgesic effect (visual analogue scale) of i.m. clonidine 2 μg kg^{-1} with the same dose of extradural clonidine after minor operations (orthopaedic or perineal surgery). Both onset and duration of analgesia after i.m. clonidine were comparable with extradural clonidine. In addition, although the peak plasma concentration of clonidine was greater in the i.m. group, side effects, including hypotension, bradycardia and drowsiness, were similar. Another possible route of systemic administration of alpha$_2$ agonists for postoperative analgesia is i.v. Tryba, Zenz and Strumpf [145] reported that clonidine 150 μg i.v., produced a similar analgesic effect to morphine 5 mg, in patients after orthopaedic operations. However, Striebel, Gottschalk and Kramer [139] could not demonstrate an analgesic effect of clonidine in patients after cholecystectomy. Aho and co-workers

[7] compared the analgesic effect of i.v. dexmedetomidine 0.2 and 0.4 μg kg^{-1} with that of oxycodone 60 μg kg^{-1} or diclofenac 250 μg kg^{-1} in women undergoing laparoscopic tubal ligation. They showed that dexmedetomidine 0.4 μg kg^{-1} produced a comparable effect to oxycodone, but drowsiness and bradycardia were present in the dexmedetomidine groups which, they suggested, may limit its usefulness. On the other hand, Bernard and colleagues [13] documented the efficacy of i.v. clonidine after major surgery. Their clonidine treatment regimen (5 μg kg^{-1} infused in the first 1 h followed by 0.3 μg kg^{-1} h^{-1}) was effective for pain relief in patients after extensive spinal surgery. They cautioned that adequate filling pressure must be maintained to prevent arterial pressure reduction.

Perioperative, as well as postoperative, administration of clonidine may decrease oxygen consumption and episodes of shivering during recovery from anaesthesia [39, 116, 117]. This feature provides further justification for using this agent in patients with coronary artery disease [57].

Miscellaneous usage. Because of their potent analgesic properties, alpha$_2$ agonists may be useful in the relief of pain other than in the postoperative period. Extradural clonidine produces effective analgesia in a dose-dependent fashion (100–900 μg) in patients with neuropathic pain with few side effects [48]. Extradural clonidine is a useful therapeutic adjunct in the management of patients with refractory reflex sympathetic dystrophy also [119]. Anecdotal reports demonstrate that intrathecal clonidine in combination with morphine or hydromorphine may attenuate cancer pain as well as opioids alone, and the combination was an excellent alternative approach to control of terminal pain [33, 52]. One case report suggested that intrathecal clonidine is effective, even if tolerance to intrathecal morphine has developed [34]. This phenomenon indicates the possibility that temporary pain control may be provided by clonidine to allow the morphine tolerant patient to recapture their sensitivity to morphine.

ACKNOWLEDGEMENTS

This work was supported in part by grants from the Uehara Memorial Fund (Y.H.), Dean's Scholarship Fund (Y.H.), NIH (M.M.) and the Department of Veterans Affairs (M.M.).

REFERENCES

1. Aantaa RE, Jaakola ML, Kallio A, Kanto J, Scheinin M, Vuorinen J. A comparison of dexmedetomidine, an α_2 adrenoceptor agonist, and midazolam as i.m. premedication for minor gynaecological surgery. *British Journal of Anaesthesia* 1991; **67**: 402–409.
2. Aantaa RE, Kanto J, Scheinen H. Intramuscular dexmedetomidine, a novel α_2 adrenoceptor agonist, as premedication for minor gynaecological surgery. *Acta Anaesthesiologica Scandinavica* 1991; **35**: 283–288.
3. Aantaa RE, Kanto JH, Scheinen M, Kallio AM, Scheinen H. Dexmedetomidine premedication for minor gynecological surgery. *Anesthesia and Analgesia* 1990; **70**: 407–413.
4. Aantaa RE, Kanto JH, Scheinen M, Kallio AM, Scheinen H. Dexmedetomidine, an α_2 adrenergic agonist, reduces anesthetic requirements for patients undergoing minor gynecological surgery. *Anesthesiology* 1990; **73**: 230–235.
5. Ahlquist RP. A study of the adrenotropic receptors. *American Journal of Physiology* 1948; **153**: 586–600
6. Aho M, Erkola OA, Scheinen H, Lehtinen AM, Kortikka KT. Effect of intravenous administered dexmedetomidine on pain after laparoscopic tubal ligation. *Anesthesia and Analgesia* 1991; **73**: 112–118.
7. Aho M, Lehtinen AM, Erkola O, Kallio A, Kortilla K. The effects of intravenous administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; **74**: 112–118.
8. Anderson RJ, Hart GR, Crumpler CP, Lerman MJ. Clonidine overdoses: Report of six cases and review of the literature. *Annals of Emergency Medicine* 1989; **10**: 107–112.
9. Angel I, Langer SZ. Adrenergic-induced hyperglycaemia in anaesthetized rats. Involvement of peripheral α_2 adrenoceptors. *European Journal of Pharmacology* 1988; **154**: 191–196.
10. Ashton H. Benzodiazepine withdrawal: Outcome in 50 patients. *British Journal of Addiction* 1987; **82**: 665–671.
11. Bailey PL, Sperry RJ, Johnson GK, Eldredge SJ, East TH, Pace NL, Stanley TH. Respiratory effects of clonidine alone and combined with morphine in humans. *Anesthesiology* 1991; **74**: 43–48.
12. Benhamou D, Veillette Y, Narchi P, Ecoffey C. Ventilatory effects of premedication with clonidine. *Anesthesia and Analgesia* 1991; **73**: 799–803.
13. Bernard JM, Hommeril JL, Passuti N, Pinaud M. Postoperative analgesia by intravenous clonidine. *Anesthesiology* 1991; **75**: 577–582.
14. Berthelsen S, Pettinger WA. A functional basis for classification of adrenergic receptors. *Life Sciences* 1977; **21**: 595–606
15. Blandiaai C, Bernardini MC, Vizi ES, Del Tacca M. Modulation of gastric acid secretion by peripheral presynaptic α_2 adrenoceptors at both sympathetic and parasympathetic pathways. *Journal of Autonomic Pharmacology* 1990; **10**: 305–312.
16. Bloor BC, Flack WE. Reduction in halothane anesthetic requirement by clonidine, an α_2 adrenergic agonist. *Anesthesia and Analgesia* 1982; **61**: 741–745.
17. Bonnet F, Boico O, Rostaing S, Loriferne JF, Saada M. Clonidine-induced analgesia in postoperative patients: Epidural versus intramuscular administration. *Anesthesiology* 1990; **72**: 423–427.
18. Bonnet F, Boico O, Rostaing S, Saada M, Loriferne JF, Touboul C, Abhay K, Ghignone M. Extradural clonidine analgesia in postoperative patients. *British Journal of Anaesthesia* 1989; **63**: 465–469.
19. Bonnet F, Brun-Buisson V, Saada M, Boico M, Rostaing S, Touboul C. Dose-related prolongation of hyperbaric tetracaine spinal anesthesia by clonidine in humans. *Anesthesia and Analgesia* 1989; **68**: 619–622.
20. Bousquet P, Feldman J, Schwartz, J. Central cardiovascular effects on adrenergic drugs: Differences between catecholamines and imidazolines. *Journal of Pharmacology and Experimental Therapeutics* 1984; **230**: 232–236.
21. Bousquet P, Feldman J, Tibirica E, Brica G, Molines A, Dontenwill M, Belcourt A. New concepts on the central regulation of blood pressure. *American Journal of Medicine* 1989; **87**: 10S–13S.
22. Brown DA. G-proteins and potassium currents in neurons. *Annual Review of Physiology* 1990; **52**: 215–242.
23. Bylund DB. Subtypes of α_2-adrenoceptors: pharmacological and molecular biological evidence converge. *Trends in Pharmacological Sciences* 1988; **9**: 356–361.
24. Bylund DB, U'Pritchard DC. Characterization of alpha-1 and alpha-2 adrenergic receptors. *International Review of Neurobiology* 1983; **24**: 343–431
25. Carabine UA, Milligan KR, Moore J. Extradural clonidine and bupivacaine for postoperative analgesia. *British Journal of Anaesthesia* 1992; **68**: 132–135.
26. Carabine UA, Milligan KR, Moore JA. Adrenergic modulation of preoperative anxiety: A comparison of temazepam, clonidine and timolol. *Anesthesia and Analgesia* 1991; **73**: 633–637.

27. Carabine UA, Milligan KR, Mulholland D, Moore J. Extradual clonidine infusions for analgesia after total hip replacement. *British Journal of Anaesthesia* 1992; **68**: 338–343.
28. Carabine UA, Wright PMC, Moore J. Preanaesthetic medication with clonidine: a dose-response study. *British Journal of Anaesthesia* 1991; **67**: 79–83.
29. Casey PJ, Gilman AG. G protein involvement in receptor–effector coupling. *Journal of Biological Chemistry* 1988; **263**: 2577–2580.
30. Chen M, Lee J, Huang BS, Grekin RJ, Malvin RL. Clonidine and morphine increase atrial natriuretic peptide secretion in anesthetized rats. *Proceedings of the Society for Experimental Biology and Medicine* 1989; **191**: 299–303.
31. Chillian WN. Functional distribution of α_1 and α_2 adrenergic receptors in coronary microcirculation. *Circulation* 1991; **84**: 2108–2122.
32. Cocks TM, Angus JA. Endothelium-dependent relaxation of coronary arteries by noradrenaline and serotonin. *Nature (London)* 1983; **305**: 627–630.
33. Coombs D, Saunder RL, Fratkin JD, Tensen LE, Mupphy CA. Continuous intrathecal hydromorphine and clonidine for intractable cancer pain. *Journal of Neurosurgery* 1986; **64**: 890–894.
34. Coombs D, Saunders RI, Lachance D, Savage S, Ragnarsson TS, Jensen LE. Intrathecal morphine tolerance: Use of intrathecal clonidine, DADLE, and intraventricular morphine. *Anesthesiology* 1985; **62**: 358–363.
35. Correa-Sales C, Rabin B, Maze M. A hypnotic response to dexmedetomidine, an α_2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992; **76**: 948–952.
36. Cushman P Jr, Sowers JR. Alcohol withdrawal syndrome: Clinical and hormonal responses to α_2 adrenergic treatment. *Alcoholism* 1989: **13**: 361–364.
37. De Jonge A, Timmermans PBMWM, Van Zweiten PA. Participation of cardiac presynaptic α_2 adrenoceptors in the bradycardic effects of clonidine and analogues. *Naunyn Schmiedebergs Archives of Pharmacology* 1981; **317**: 8–12.
38. Dekock M, Pichon G, Scholtes JL. Intraoperative clonidine enhances postoperative morphine patient controlled analgesia. *Anesthesiology* 1991; **75**: A654.
39. Delaunay L, Bonnet F, Duvaldestin P. Clonidine decreases postoperative oxygen consumption in patients recovering from general anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 397–401.
40. Deveasa J, Arce V, Lois N, Tresquerres AF, Lima L. α_2 adrenergic agonism enhances the growth hormone (GH) response to GH-releasing hormone through an inhibition of hypothalmic somatostatin release in normal man. *Journal of Clinical Endocrinology and Metabolism* 1990; **71**: 1581–1588.
41. Deveasa J, Diaz MJ, Tresquerres AI, Arce V, Lima L. Evidence that α_2 adrenergic pathways play a major role in growth hormine (GH) neuroregulation: α_2 adrenergic agonism counteracts the inhibitory effects of muscarinic cholinergic receptor blockade on the GH response to GH-releasing hormone, while α_2 adrenergic blockade diminishes the potentiating effect of increased cholinergic tone on such stimulation in normal men. *Journal of Clinical Endocrinology and Metabolism* 1991; **73**: 251–256.
42. Dohlman HG, Thorner J, Caron MG, Lefkowitz RJ. Model systems for the study of seven-transmembrane-segment receptors. *Annual Review of Biochemistry* 1991; **60**: 653–688.
43. Doze VA, Chen BX, Maze M. Dexmedetomidine produces a hypnotic–anesthetic action in rats via activation of central α_2 adrenoceptors. *Anesthesiology* 1989; **71**: 75–79.
44. Drew GM, Whiting SB. Evidence for two distinct types of postsynaptic alpha-adrenoceptors in vascular smooth muscle in vivo. *British Journal of Pharmacology* 1979; **67**: 207–215.
45. Dukes ID, Williams EMV. Effects of selective α_1-, α_2-, β_1- and β_2-adrenoceptor stimulation on potentials and contractions in the rabbit heart. *Journal of Physiology (London)* 1984; **355**: 523–546.
46. Eisenach J, Lysak SZ, Viscomi CM. Epidural clonidine analgesia following surgery: Phase 1. *Anesthesiology* 1989; **71**: 640–646.
47. Eisenach JC. Intravenous clonidine produces hypoxia by a peripheral α_2 adrenergic mechanisn. *Journal of Pharmacology and Experimental Therapeutics* 1988; **244**: 247–252.
48. Eisenach JC, Rauck RL, Buzzanell C, Lysak S. Epidural clonidine analgesia for intractable cancer pain: Phase 1. *Anesthesiology* 1989; **71**: 647–652.
49. Engelman E, Lipszyc M, Gilbart E, Van der Linden P, Bellens B, Van Romphey A, deRood M. Effects of clonidine on anesthetic requirements and hemodynamic response during aortic surgery. *Anesthesiology* 1989; **71**: 178–187.
50. Ernsberger P, Guiliano R, Willette N, Reis D. Role of imidazole receptors in the vasodepressor response to clonidine analogs in the rostal ventrolateral medulla. *Journal of Pharmacology and Experimental Therapeutics* 1990; **253**: 408–418.
51. Ernsberger P, Meeley MP, Mann JJ, Reis DJ. Clonidine binds to imidazoline binding sites as well as α_2-adrenoceptors in the ventrolateral medulla. *European Journal of Pharmacology* 1987; **134**: 1–13.
52. van Essen EJ, Bovill JG, Ploeger EJ, Beerman H. Intrathecal morphine and clonidine for control of intractable cancer pain. A case report. *Acta Anaesthesiologica Belgica* 1988; **39**: 109–112.
53. van Essen EJ, Bovill JG, Ploeger EJ, Houben JJG. Pharmacokinetics of clonidine after epidural administration in surgical patients. Lack of correlation between plasma concentration and analgesia and blood pressure changes. *Acta Anaesthesiologica Scandinavia* 1992; **36**: 300–304.
54. Ferrari F, Tartoni PL, Margiafico V. B-HT 920 antagonizes rat neophobia in the X-Maze test. *Archives Internationales de Pharmacodynamie et de Therapie* 1989; **298**: 71–74.
55. Fielding S, Wilker J, Hynes M, Szewczak M, Novick WJ jr, Lal H. A comparison of clonidine with morphine for antinociceptive and anti-withdrawal actions. *Journal of Pharmacology and Experimental Therapeutics* 1978; **207**: 899–905.
56. Filos KS, Goudas LC, Patroni O, Polyzou V. Intrathecal clonidine as a sole analgesic for pain relief after cesarean section. *Anesthesiology* 1992; 77: 174–267.
57. Flack JW, Bloor BC, Flack WE, Wong D, Dazza S, Stead SW, Laks H. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary surgery. *Anesthesiology* 1987; **67**: 11–19.
58. Garty M, Ben-Zvi Z, Harwity A. Interaction of clonidine and morphine with lidocaine in mice and rats. *Toxicology and Applied Pharmacology* 1989; **101**: 255–260.
59. Ghingnone M, Calvillo O, Quintin L. Anesthesia and hypertension: The effect of clonidine on preoperative hemodynamics and isoflurane requirements. *Anesthesiology* 1987; **67**: 3–10.
60. Ghingnone M, Calvillo O, Quintin L. Anesthesia for ophthalmic surgery in the elderly: The effects of clonidine on intraocular pressure, perioperative hemodynamics, and anesthesia requirement. *Anesthesiology* 1988; **68**: 707–716.
61. Ghingnone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal induction. *Anesthesiology* 1986; **64**: 36–42.
62. Gold MS, Redmond DE Jr, Kleber HD. Clonidine blocks acute opiate withdrawal symptoms. *Lancet* 1978; **2**: 599–602.
63. Gordh T Jr. Epidural clonidine for treatment of postoperative pain after thoracotomy. A double-blind placebo-controlled study. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 702–709.
64. Grossman A, Weerasuriya K, Al-Damluji S, Turner P, Besser GM. Alpha$_2$ adrenoceptor agonists stimulate growth hormone secretion but have no acute effects on plasma cortisol under basal conditions. *Hormone Research* 1987; **25**: 65–71.
65. Gustafson I, Westerberg E, Wielock T. Protection against ischemia-induced neural damage by the alpha$_2$-adrenoceptor antagonist idazoxan: Influence of time of administration and possible mechanism of action. *Journal of Cerebral Blood Flow and Metabolism* 1990; **10**: 885–894.
66. Gustafson I, Yoshimoto M, Wieloch TW. Postischemic administration of idazoxan, an alpha$_2$ adrenergic receptor antagonist, decreased neuroral damage in the rat brain. *Journal of Cerebral Blood Flow and Metabolism* 1989; **9**: 171–174.
67. Gutman Y, Boonyaviroj P. Suppression by noradrenaline of catecholamine secretion from adrenal medulla. *European Journal of Pharmacology* 1974; **28**: 384–386.

68. Hayashi Y, Kamibayashi T, Maze M, Yamatodani A, Sumikawa K, Kuro M, Yoshiya I. Contribution of imidazoline preferring receptors to the modulation of halothane-epinephrine arrhythmias in dogs. *Anesthesiology* 1992; **77**: A667.
69. Hayashi Y, Sumikawa K, Maze M, Yamatodani A, Kamibayashi T, Kuro M, Yoshiya I. Dexmedetomidine prevents epinephrine-induced arrhythmias through stimulation of central alpha$_2$ adrenoceptors in halothane-anesthetized dogs. *Anesthesiology* 1991; **75**, 113–117.
70. Heusch G, Schipke J, Thamer V. Clonidine prevents sympathetic initiation and aggravation of poststenotic myocardial ischemia. *Journal of Cardiovascular Pharmacology* 1985; **7**: 1176–1182.
71. Hoffman WE, Cheng MA, Thomas C, Baughman VL, Albrecht RF. Clonidine decreases plasma catecholamines and improves outcome from incomplete ischemia in the rat. *Anesthesia and Analgesia* 1991; **73**: 460–464.
72. Hoffman WE, Kochs E, Werner C, Thomas C, Albrecht RF. Dexmedetomidine improves neurologic outcome from incomplete ischeme in the rat. *Anesthesiology* 1991; **75**: 328–332.
73. Hori M, Kitakaze M, Tamai J, Iwakura K, Kitabatake A, Inoue M, Kamada T. Alpha$_2$-adrenoceptor stimulation can augment coronary vasodilation maximally induced by adenosine in dogs. *American Journal of Physiology* 1989; **257**: H140–H142.
74. Housemans PR. Effects of dexmedetomidine on contractility, relaxation and intracellular calcium transients of isolated ventricular myocardium. *Anesthesiology* 1990; **73**: 919–922.
75. Jaakola ML, Ali-Melkkila T, Kanto J, Kallio A, Scheinin H, Scheinin M. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. *British Journal of Anaesthesia* 1992; **68**: 570–575.
76. Jaakola ML, Salonen M, Lehinen R, Scheinin H. The analgesic action of dexmedetomidine a novel alpha$_2$-adrenoceptor agonist in healthy volunteers. *Pain* 1991; **46**: 281–285.
77. Javis DA, Duncan SR, Segal IS, Maze M. Ventilatory effects of clonidine alone and in the presence of alfentanil, in human volunteers. *Anesthesiology* 1992; **76**: 899–905.
78. Kamibayashi T, Hayashi Y, Sumikawa K, Yamatodani A, Yoshiya I. A role of vagus nerve in antiarrhythmic effects of doxazosin and dexmedetomidine on halothane–epinephrine arrhythmias. *Anesthesiology* 1992; **77**: A642.
79. Karhuvaara S, Kallio AM, Salonen M, Tuominen J, Scheinin M. Rapid reversal of alpha$_2$-adrenoceptor agonist effects by atipamezole in human volunteers. *British Journal of Clinical Pharmacology* 1991; **31**: 160–165.
80. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha$_2$-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. *Anesthesia and Analgesia* 1990; **71**: 25–29.
81. Kaukinen S, Pyykko K. The potentiation of halothane anesthesia by clonidine. *Acta Anaesthesiologica Scandinavica* 1979; **23**: 107–111.
82. Kauppila T, Kemppainen P, Tanila H, Pertovaara A. Effect of systemic medetomidine, an alpha$_2$ adrenoceptor agonist, on experimental pain in humans. *Anesthesiology* 1991; **74**: 3–8.
83. Krieglstein GK, Langhan ME, Lydhecker W. The principal and central neural actions of clonidine in normal and glaucomatous eyes. *Investigative Ophthalmology* 1978; **17**: 149–158.
84. Kubo T, Misu Y. Pharmacological characterization on the α-adrenoceptor responsible for a decrease of blood pressure in the nucleus tractus solitari of the rat. *Naunyn Schmiedebergs Archives of Pharmacology* 1981; **317**: 120–125.
85. Kumar A, Bose S, Phattacharya A, Tandon OP, Kundra P. Oral clonidine premedication for elderly patients undergoing intraocular surgery. *Acta Anaesthesiologica Scandinavica* 1992; **36**: 159–164.
86. Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG Jr. Differentiation of receptor systems activated by sympathomimetic amines. *Nature (London)* 1967; **214**: 597–598.
87. Langer SZ. Presynaptic regulation of catecholamine release. *Biochemical Pharmacology* 1974; **23**: 1793–1800.
88. Levitzki A. From epinephrine by cyclic AMP. *Science* 1988; **241**: 800–806.
89. Lindgren BR, Ekstrom T, Anderson RG. The effect of inhaled clonidine in patients with asthma. *American Review of Respiratory Disease* 1986; **134**: 266–269.
90. McArthur KE, Anderson DS, Durbin TE, Orloff MJ, Dharmsathaphorn K. Clonidine and lidamidine to inhibit watery diarrhea in a patient with lung cancer. *Annals of Internal Medicine* 1982; **96**: 323–325.
91. McPherson RW, Traystman RJ. Effect of dexmedetomidine on cerebrovascular response to hypoxia during isoflurane anesthesia. *Anesthesiology* 1991; **75**: A174.
92. Maiese K, Pek L, Berger SB, Reis DJ. Reduction in focal cerebral ischemia by agents acting at imadazole receptors. *Journal of Cerebral Blood Flow and Metabolism* 1992; **12**: 53–63.
93. Massara F, Limone P, Cagliero E, Tagliabue M, Isaia GC, Molinatti GM. Effects of naloxone on the insulin and growth hormone responses to alpha-adrenergic stimulation with clonidine. *Acta Endocrinologica* 1983; **103**: 371–375.
94. Maze M, Vickery RG, Merlone SC, Gaba DM. Anesthetic and hemodynamic effects of the alpha$_2$ adrenergic agonists, azepexole, in isoflurane-anesthetized dogs. *Anesthesiology* 1988; **68**: 689–694.
95. Maze M, Virtanen R, Daunt D, Banks SJM, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole sedative–anesthetic agent, on adrenal stereogenesis: in vivo and in vitro studies. *Anesthesia and Analgesia* 1991; **73**: 204–208.
96. Mendez R, Eisenach JC, Kashtan K. Epidural clonidine analgesia after cesarean section. *Anesthesiology* 1990; **73**: 848–852.
97. Miyamoto MI, Rockman HA, Guth BD, Heusch G, Ross J Jr. Effect of alpha-adrenergic stimulation on regional contractile function and myocardial blood flow with and without ischemia. *Circulation* 1991; **84**: 1715–1724.
98. Nguyen D, Abdul-Rasool I, Ward D, Hsieh J, Kobayashi D, Hadlock S, Singer F, Bloor B. Ventilatory effects of dexmedetomidine, atipamezole, and isoflurane in dogs. *Anesthesiology* 1992; **76**: 573–579.
99. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. *Anesthesiology* 1990; **73**: 853–859.
100. Nishikawa T, Dohi S. Oral clonidine blunts the heart rate response to intravenous atropine in humans. *Anesthesiology* 1991; **75**: 217–222.
101. Nishikawa T, Kimura T, Taguchi N, Dohi S. Oral clonidine preanesthetic medication augments the pressor responses to intravenous ephedrine in awake or anesthetized patients. *Anesthesiology* 1991; **74**: 705–710.
102. Olsson JM, Pruitt AW. Management of clonidine ingestion in children. *Journal of Pediatrics* 1983; **103**: 646–650.
103. Omote K, Kitahata L, Collins JG, Nakatani K, Nakagawa I. Interaction between opiate subtype and alpha$_2$ adrenergic agonists in suppression of noxiously evoked activity of WDR neurons in the spinal dorsal horn. *Anesthesiology* 1991; **74**: 737–743.
104. Orko R, Pouttu J, Ghignone M, Rosenberg PH. Effect of clonidine on haemodynamic responses to endotracheal intubation and gastric acidity. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 325–329.
105. Ossipov MH, Harris S, Lloyd P, Messineo E, Lin BS, Bagley J. Antinoceptive interaction between opioids and medetomidine: system additivity and spiral synergy. *Anesthesiology* 1990; **73**: 1227–1235.
106. Ota K, Namiki A, Ujike Y, Takahashi I. Prolongation of tetracaine spinal anesthesia by oral clonidine. *Anesthesia and Analgesia* 1992; **75**: 262–264.
107. Paalzow G. Development of tolerance to the analgesic effect of clonidine in rats. Cross-tolerance to morphine. *Naunyn Schmiedebergs Archives of Pharmacology* 1978; **304**: 1–4.
108. Paton WD, Vizi ES. The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strip. *British Journal of Pharmacology* 1969; **35**: 10–28.
109. Penon C, Ecoffey C, Cohen SE. Ventilatory response to carbon dioxide after epidural clonidine injection. *Anesthesia and Analgesia* 1991; **72**: 761–764.

110. Pertovaara A, Kauppila T, Jyasjarvi E, Kalso E. Involvement of supraspinal and spinal segmental alpha-2-adrenergic mechanisms in the medetomidine-induced antinociception. *Neuroscience* 1991; **44**: 705–714.
111. Peskind ER, Raskind MA, Leake RD, Ervin MG, Ross MG, Dorsa DM. Clonidine decreases plasma and cerebrospinal fluid arginine vasopressin but not oxytocin in humans. *Neuroendocrinology* 1987; **46**: 395–400.
112. Pluskwa F, Bonnet F, Saada M, Macquin-Mavier I, Becquemin JP, Catoire P. Effects of clonidine on variation of arterial blood pressure and heart rate during carotid artery surgery. *Journal of Cardiothoracic Vascular Anesthesia* 1991; **5**: 431–436.
113. Potter D, Ogidigben MJ. Medetomidine-induced alterations of intraocular pressure and contraction of the nictitating membrane. *Investigative Ophthalmology of Visual Science* 1991; **32**: 2799–2805.
114. Powis DA, Baker PF. Alpha$_2$-adrenoceptors do not regulate catecholamine secretion by bovine adrenal medullary cells: A study with clonidine. *Molecular Pharmacology* 1986; **29**: 134–141.
115. Quintin L, Bonnet F, Macquin I, Szekely B, Becquemin JP, Ghingnone M. Aortic surgery: Effect of clonidine on intraoperative catecholaminergic and circulatory stability. *Acta Anaesthesiologica Scandinavica* 1990; **34**: 132–137.
116. Quintin L, Roudot F, Roux C, Macquin I, Basmaciogullari A, Guyene T, Vaubourdolle M, Viale JP, Bonnet F, Ghignone M. Effect of clonidine on the circulation and vasoactive hormones after aortic surgery. *British Journal of Anaesthesia* 1991; **66**: 108–115.
117. Quintin L, Viale JP, Annat G, Hoen JP, Butin E, Cottet-Emard JM, Levron JC, Butin E, Cottet-Emard JM, Levron JC, Busserv D, Motin J. Oxygen uptake after major abdominal surgery: Effect of clonidine. *Anesthesiology* 1991; **74**: 236–241.
118. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesthesia and Analgesia* 1987; **66**: 442–446.
119. Rauck RL, Eisenach JC, Jackson KE, Speight KL, Southern BSN. Epidural clonidine for refractory reflex sympathetic dystrophy. *Anesthesiology* 1991; **75**: A657.
120. Regunathan S, Evinger MJ, Meeley M, Reis D. Effects of clonidine and other imidazole-receptor binding agents on second messenger systems and calcium influx in bovine adrenal chromaffin cells. *Biochemical Pharmacology* 1991; **42**: 2011–2018.
121. Richard MJ, Skues MA, Jarvis AP, Prys-Roberts C. Total i.v. anaesthesia with propofol and alfentanil: dose requirements for propranolol and the effect of premedication with clonidine. *British Journal of Anaesthesia* 1990; **65**: 157–163.
122. Ross CA, Ruggiero DA, Reis DJ. Projections from the nucleus tractus solitarii to the rostal ventrolateral medulla. *Journal of Comparative Neurology* 1985; **242**: 511–534.
123. Rostaing S, Bonnet F, Levron JC, Vodinh J, Pluskwa F, Saada M. Effects of epidural clonidine on analgesia and pharmacokinetics of epidural fentanyl in postoperative patients. *Anesthesiology* 1991; **75**: 420–425.
124. Ruffolo RR, Nichols AJ, Hieble JP. Functions mediated by alpha$_2$ adrenergic receptors. In: Limbird LE, ed. *The Alpha$_2$ Adrenergic Receptors*. Clifton, NJ: Humana Press, 1988; 187–280.
125. Ruffolo RR Jr. Distribution and function of peripheral alpha-adrenoceptors on the cardiovascular system. *Pharmacology, Biochemistry and Behavior* 1985; **22**: 827–833.
126. Salonen M, Reid K, Maze M. Synergistic interaction between alpha$_2$-adrenergic agonists and benzodiazepines in rats. *Anesthesiology* 1992; **76**: 1004–1011.
127. de Sarro GB, Ascioti C, Froio F, Libri V, Nistico G. Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha$_1$ and alpha$_2$ adrenoceptors affect sleep and arousal mechanisms. *British Journal of Pharmacology* 1987; **90**: 675–685.
128. Scheinin B, Lindgren L, Randel T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduced the need for thiopentone and preoperative fentanyl. *British Journal of Anaesthesia* 1992; **68**: 126–131.
129. Scheinin H, Virtanen R, MacDonald E, Lammintausta R, Scheinin M. Medetomidine—a novel α_2-adrenoceptor agonist: a review of its pharmacodynamic effects. *Progress in Neuropsychopharmacology and Biological Psychiatry* 1989; **13**: 635–651.
130. Schmeling WT, Kampine JP, Roerig DL, Warltier DC. The effects of the stereoisomers of the alpha$_2$ adrenergic agonist medetomidine on systemic and coronary hemodynamics in conscious dogs. *Anesthesiology* 1991; **75**: 499–511.
131. Segal IS, Javis DJ, Duncan SR, White PF, Maze M. Clinical efficacy of oral–transdermal clonidine combinations during the perioperative period. *Anesthesiology* 1991; **74**: 220–225.
132. Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha$_2$ adrenergic receptors. *Anesthesiology* 1988; **69**: 818–823.
133. Soderpalm B, Engel JA. Biphasic effects of clonidine on conflict behaviour: Involvement of different alpha-adrenoceptors. *Pharmacology, Biochemistry and Behavior* 1988; **30**: 471–477.
134. Spaulding TC, Fielding S, Venafro JJ, Lal H. Antinociceptive activity of clonidine and its potentiation of morphine analgesia. *European Journal of Pharmacology* 1979; **58**: 19–25.
135. Stanton B, Puglisi E, Gellai M. Localization of alpha$_2$-adrenoceptor-mediated increase in renal Na^+, K^+, and water excretion. *American Journal of Physiology* 1987; **252**: F1016–1021.
136. Stevens CW, Monasky MS, Yaksh TL. Spinal infusion of opiate and alpha-2 agonists in rats: Tolerance and cross-tolerance studies. *Journal of Pharmacology and Experimental Therapeutics* 1988; **244**: 63–70.
137. Stiles GL, Caron MG, Lefkowitz RJ. β-adrenergic receptors: biochemical mechanisms of physiological regulation. *Physiological Reviews* 1984; **64**: 661–743.
138. Strandhoy JW. Role of alpha$_2$ receptors in the regulation of renal function. *Journal of Cardiovascular Pharmacology* 1985; 7 (Suppl. 8): S28–S33.
139. Striebel HW, Gottschalk B, Kramer J. Clonidine does not reduce postoperative meperidine requirements. *Anesthesiology* 1991; **75**: A659.
140. Sutherland EW, Rall TW. The relation of adenosine 3′:5′-cyclic phosphate and phosphorylase to the actions of catecholamines and other hormones. *Pharmacological Review* 1970; **12**: 265–299.
141. Svensson TH, Bunney BS, Aghajanian GK. Inhibition of both noradrenergic and serotonergic neurons in brain by the alpha-adrenergic agonist clonidine. *Brain Research* 1975; **92**: 291–306.
142. Tibirica E, Feldman J, Mermet C, Gonon F, Bousquet P. An midazoline-specific mechanism for the hypotensive effect of clonidine. A study with yohimbine and idazoxan. *Journal of Pharmacology and Experimental Therapeutics* 1991; **256**: 606–613.
143. Tibirica E, Feldman J, Mermet C, Monassier L, Gonon F, Bousquet P. Selectivity of rilmenidine for the nucleus reticularis lateralis, a ventrolateral medullary structure containing imidazoline-preferring receptors. *European Journal of Pharmacology* 1991; **209**: 213–221.
144. Toon S, Hopkins KJ, Aarons L, Rowland M. Rate and extent of absorption of clonidine from a transdermal therapeutic system. *Journal of Pharmacy and Pharmacology* 1989; **41**: 17–21.
145. Tryba M, Zenz M, Strumpf M. Clonidine i.v. is equally effective as morphine i.v. for postoperative analgesia—A double blind study. *Anesthesiology* 1991; **75**: A1085.
146. Tzeung JT, Wang JJ, Mok MS, Lippmann M. Clonidine potentiates lidocaine-induced epidural anesthesia. *Anesthesia and Analgesia* 1989; **68**: S298.
147. Uhde TW, Stein MB, Vittone BJ, Seiver LJ, Boulenger JP, Klein E, Mellaman TA. Behavioral and physiologic effects of short-term and long-term administration of clonidine in panic disorder. *Archives of General Psychiatry* 1989; **46**: 170–177.
148. Unnerstall J, Kopajtic TA, Kuhar MJ. Distribution of alpha$_2$ agonists binding sites in the rat and human central nervous system. Analysis of some functional, autonomic

correlates of the pharmacology effects of clonidine and related adrenergic agents. *Brain Research Review* 1984; **7**: 69–101.

149. Vickery RG, Sheridan BS, Segal IS, Maze M. Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an alpha$_2$-adrenergic agnonist, in halothane-anesthetized dogs. *Anesthesia and Analgesia* 1988; **67**: 611–615.
150. Wada A, Sakurai S, Kobayashi H, Yanagihara N, Izumi F. Alpha2-adrenergic receptors inhibit catecholamine secretion from bovine adrenal medulla. *Brain Research* 1982; **252**: 189–191.
151. Wang YC, Su CR, Lin MT. The site and mode of analgesic actions exerted by clonidine in monkeys. *Environmental Neurology* 1985; **90**: 479–488.
152. Wilcox GL, Carlsson KH, Jochim A, Jurna I. Mutual potentiation of antinociceptive effects of morphine and clonidine on motor and sensory response in rat spinal cord. *Brain Research* 1987; **405**: 84–93.
153. Wright RMC, Carabine UA, Orr DA, McClune S, Moore J. Preanaesthetic medication with clonidine. *British Journal of Anaesthesia* 1990; **65**: 628–635.
154. Yaksh TL, Reddy SVR. Studies in primate on the analgesic effects associated with intrathecal actions of opiates, alpha$_2$ adrenergic agonists, and baclofen. *Anesthesiology* 1981; **54**: 451–467.
155. Yam PC, Forbes A, Kox WJ. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. *British Journal of Anaesthesia* 1992; **68**: 106–108.
156. Zornow NH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine, and alpha$_2$-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. *Anesthesia and Analgesia* 1990; **70**: 624–630.