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The Mesenteric-Portal Vein in Research

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I. Introduction

The use of the isolated anterior MPV† was reintroduced into biological research 25 years ago. Since then it has been used by pharmacologists, physiologists, and biochemists to study smooth muscle and vascular function, to develop new drugs, and to investigate the mechanism of action of drugs, old and new. In view of its ubiquitous and continued use it seemed worthwhile to review the literature dealing with observations derived from the MPV as an experimental tissue during the last quarter century. A Medline search up to summer 1989 revealed that more than 500 original papers have been published in which findings based upon investigation of this vein in vitro have been reported. Those publications form the basis for this review.

In 1937 Franklin published a monograph in which the use of the MPV as an experimental tissue is described. He reported use of this vessel by German researchers in the 1920s and summarised his own observations of the MPV. The work of the German biologists and of Franklin was then largely forgotten until 1964 when we (Cuthbert and Sutter, 1964) and others (Funaki and Bohr, 1964) reported that this blood vessel from rabbit and rat, respectively, possessed spontaneous contractile activity accompanied by action potentials. These were the first reports of action potentials in a mammalian vein.

It was apparent that the MPV is a reliable preparation which responds rapidly to a variety of drugs, and the presence of electrical activity provided an opportunity to study both mechanical and electrical correlates as affected by drugs. It was not at all clear up to then whether stimulant or inhibitory agents acted via electrical changes. This question has been a theme that has pervaded much of the use of this blood vessel in experimentation. The introduction of the term "pharmacomechanical coupling" by the Somlyos (Somlyo and Somlyo, 1968) focussed attention on the problem, although the phenomenon had been investigated earlier (Cuthbert and Sutter, 1965).

It was suggested early on that the MPV could be used as an analogue of resistance vessels (Ljung, 1970; Rhodes and Sutter, 1971a). This was based on the observation that resistance vessels often show vasomotion, as does the MPV, and that the sensitivity of the responses of the MPV to calcium reduction was very different from that of the aorta, a conduit-type vessel. Subsequently, it was confirmed that responses of peripheral resistance vessels to noradrenaline in vivo are highly dependent on the presence of external calcium (Sutter et al., 1977). It may well be that the MPV functionally resembles resistance vessels in several ways.

† Abbreviations: MPV, mesenteric-portal vein; S-R, sarcoplasmic reticulum; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; VIP, vasoactive intestinal polypeptide; Tris, tris(hydroxymethyl)aminomethane; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; PCr, phosphocreatine; EDRF, endothelium-dependent relaxing factor; PAF-acether, platelet-activating factor; SHR, spontaneously hypertensive rat; WKY, Wistar-Kyoto rat; RHR, one-clip renal hypertensive rat; DOCA, desoxycorticosterone.

Examination of the literature reveals that the terminology can vary when naming the tissue used for experimentation. We (Sutter, 1965; Cuthbert and Sutter, 1965) used the term anterior mesenteric vein in our reports, whereas others (Holman and McLean, 1967) and the group in Gothenberg (Axelsson et al., 1967; Johansson et al., 1967; Johansson and Ljung, 1967) used the term portal vein. It is likely that the groups were using the same preparation because the portal vein is formed by the junction of anterior mesenteric and splenic vein and the course of the portal vein is short. In any event, no distinction will be made in this review between portal and anterior mesenteric vein. There also were dissimilarities in the preparation of the tissue in that whole veins (Johansson and Ljung, 1967), everted whole veins (Mastrangelo and Mathison, 1983), and spiral strips (Alexander, 1967a) were used. It was earlier reported that the bulk of the smooth muscle was oriented longitudinally (Sutter, 1965) and longitudinal strips or whole veins mounted longitudinally have become the usual preparation.

Various preparations of the whole vein also have been used. The MPV of the dog was used as a closed system or isolated sac with the distal end tied off and the proximal end fixed to a pipette. The effects of noradrenaline, serotonin, and tyramine on its capacity were studied (Clement and Vanhoutte, 1967). All three agents reduced the volume of the venous bag as measured by displacement of fluid into the pipette. Phentolamine antagonised the effects of all three, whereas cocaine interfered with the effects of tyramine, thus demonstrating the direct effects of noradrenaline and serotonin but indirect effects of tyramine.

The MPV of the mouse has been used as an isolated perfused preparation and the effects of noradrenaline and acetylcholine have been examined (Helfer and Jaques, 1970). Both drugs decreased the compliance of this system.

The animal species from which the MPV has been examined in vitro varies from mouse (Mislin, 1968), hedgehog (Eliassen and Helle, 1975), and rainbow lizard (Ojewole, 1983) to horse (Dacquet et al., 1989). Similarly, the techniques applied to the MPV range from nerve-muscle preparations (Ljung, 1969) to tissue homogenates and ligand-binding assays (Dacquet et al., 1989).

I have organised this review into somewhat arbitrary sections to attempt to depict coherently the research that has been done. Each section refers to articles that present data obtained from the MPV and are pertinent to the heading. Several articles, of course, contain information that is relevant to more than one section. Whether the data and conclusions can be generalised to smooth muscles other than the MPV is left to the reader to decide.

II. Structure and Constituents

A. Muscle Orientation

Franklin (1937) pointed out in his monograph that the MPV possessed two distinct layers, an outer longitudinal and an inner circular muscular coat. That observation was confirmed for rabbit (Sutter, 1965), sheep (Holman and McLean, 1967), and rat (Ts'ao et al., 1970) MPV. It also has been reported (McConnell and Roddie, 1970) that longitudinal strips, but not rings, prepared from MPV of cows showed spontaneous activity. The responses of circular and longitudinal muscle of dog MPV were also examined in a perfused preparation (Hall and O'Connor, 1973). The responses to agonists differed in the two types of muscle.

Further comparison of preparations of longitudinal and circular muscle was done by Cohen and Wiley (1977a) and by Mathison (1983) using responses to a variety of vasoactive agents. Mathison concluded that the circular muscle of rat MPV was less sensitive (increased ED_{50}) to acetylcholine, 5-hydroxytryptamine, and angiotensin than was longitudinal muscle in rats. Similarly, it has been reported (Brown et al., 1982) that in the rabbit MPV circular and longitudinal muscle develop the same stress (force per unit area) to 10^{-5} M acetylcholine but differ in the stress developed in response to histamine. When the responses were normalised for the amount of muscle, 10^{-5} M histamine produced more stress in circular muscle. There also is a report (Mastrangelo and Mathison, 1983) that the ED_{50} for noradrenaline is less when everted vein is the test tissue compared to noneverted vein. This may involve access of the agonist to contractile sites because the ED_{50} for noradrenaline is similar if strips and everted vein preparations are compared. It, therefore, seems important to be aware of whether longitudinal, circular muscle or whole vein is used when comparing responses to drugs in the MPV.

A paper has recently appeared (Yoshioka et al., 1988b) in which the dissimilarities between the structure and pharmacological responses of portal and splenic vein and splenic capsule have been pointed out. The authors report that splenic capsule and portal vein resemble each other more than do splenic vein and capsule and suggest that splenic vein has different embryonic origins and is virtually inserted between the other two structures.

B. Subcellular Architecture

The subcellular structure of the MPV was first examined by Holman and colleagues (1968b) who described tight junctions between cells of rabbit MPV. The Somlyos and coworkers (Rice et al., 1971; Somlyo et al., 1971) then published a series of papers indicating that this vascular smooth muscle contained contractile proteins organised regularly into thick and thin filaments. This same group (Devine et al., 1972) compared the content of S-R in a variety of smooth muscles and found that the MPV possessed less S-R than aorta or pulmonary artery, 2.2% of volume compared to approximately 5% in the latter two tissues. This approximately parallels the dependence of these tissues on external calcium to support contraction; the aorta and pulmonary artery retain their

responses to agonists better than the MPV in the absence of added external calcium (Sigurdsson et al., 1975; Sutter, 1976). The S-R was further characterised by freeze-fracture electron microscopy (Devine and Rayns, 1975). It was described as being oriented longitudinally and related closely to mitochondria in MPV. The S-R was considered to be a possible source of intracellular calcium, but it remained for analysis with electron probe x-ray microscopy to demonstrate that calcium was localised intracellularly in sites corresponding to the S-R (Somlyo et al., 1977). Subsequent work from the same laboratory confirmed the high concentration of calcium in S-R and also showed that mitochondria contained low concentrations of calcium under normal conditions but could take up large amounts if the cell membrane was damaged (Somlyo et al., 1979).

The subcellular organisation of the MPV also has been examined by Burnstock and coworkers (Komuro and Burnstock, 1980). They described the appearance of intercellular regions and reported that the inner circular muscle had many more branches than the outer longitudinal muscle. Gap junctions were described in both layers of muscle.

C. Ions

The Somlyos refined the use of electron probe x-ray microscopy and combined it with functional studies to examine the localisation of calcium during the contraction cycle. They (Bond et al., 1984a) reported that calcium could be recycled from the S-R during repeated contractions induced by noradrenaline in guinea pig MPV, but it must be noted that special circumstances pertained in those functional studies. Lanthanum was present in the bath fluid, the temperature was 23°C, and the agonist was washed out before the peak of contraction was reached. The same group (Bond et al., 1984b) also looked at the distribution of calcium during contraction and relaxation and found that cytoplasmic calcium increased during contraction of the rabbit MPV.

The subcellular concentration of ions other than calcium as determined by electron probe microanalysis was also reported by the Somlyo group (Somlyo et al., 1985). Of particular interest was their finding of high cytoplasmic chloride. This is consistent with cells in the MPV being rather permeable to chloride as reported by Wahlström (1973a).

The ultrastructural effect of increased extracellular potassium also has been examined in rabbit MPV (Jones et al., 1973). KCl, 150 mM, and K_2SO_4, 180 mM, were equieffective in causing contraction. KCl, however, caused marked swelling of smooth muscle cells and loss of myofilaments, whereas K_2SO_4 caused shrinkage of cells and much less loss of myofilaments. The structural requirements for functional myofilaments, therefore, are uncertain.

D. Summary

There are two layers of muscle in the MPV, an outer longitudinal layer and an inner circular layer. The contractility, responses to stimuli and structure can differ in the two layers. The S-R is relatively sparse in the MPV and contains a relatively high concentration of calcium. The mitochondria do not contain much calcium ordinarily. Chloride content of the sarcoplasm is relatively high.

III. Innervation and Transmitters

A. Adrenergic Innervation

The first report of the nature of the innervation of the MPV was by Holman and McLean (1967) who used the Falck technique of fluorescent histochemistry to demonstrate that this vessel contained adrenergic nerve endings. Subsequently, a similar study was done on the rat MPV (Booz, 1971). A nerve-muscle preparation of the rat MPV was developed by Ljung (Ljung, 1969) and he compared equieffective responses to applied noradrenaline and to nerve stimulation. He calculated that nerve stimulation at 4 and 16 Hz, respectively, gave responses equivalent to concentrations of noradrenaline of approximately 8×10^{-6} and 2×10^{-5} M.

Synthesis of catecholamines was studied in rabbit MPV using [^{14}C]tyrosine (Gillis and Roth, 1970) and these workers found that the MPV synthesised noradrenaline at a rate of 270 ng/g/h, whereas the synthesis rate in the aorta was much slower (68 ng/g/h) and mesenteric artery was much faster (630 ng/g/h). The release of noradrenaline in response to transmural stimulation was found to be enhanced by angiotensin II (Hughes and Roth, 1971), whereas uptake of or response to exogenous noradrenaline was not affected. It subsequently was found that angiotensin II also increased the synthesis of noradrenaline in guinea pig and rat, but not rabbit, MPV (Boadle-Biber et al., 1972). Angiotensin III also enhanced the release of noradrenaline in response to transmural stimulation in rabbit MPV (Trachte et al., 1984). Therefore, more than one angiotensin receptor may be involved (Trachte et al., 1984).

The relative roles of neuronal and extraneuronal uptake of noradrenaline have been studied in rat MPV (Hedner et al., 1981) and extraneuronal uptake was found to be more prominent at high concentrations of exogenous noradrenaline. There was a report that suggested that activity of sympathetic nerves can increase tyrosine hydroxylase activity in rabbit MPV (Takimoto and Weiner, 1981). The evidence is that hexamethonium prevented the increased activity of this enzyme which ordinarily occurred when the animal was decapitated.

The effect of inhibition of monoamine oxidase by pargyline was studied in the guinea pig by Berkowitz et al. (1974). They found that synthesis of noradrenaline was inhibited by 70–86% in MPV but only 46% in

mesenteric artery, presumably due to less feedback inhibition by accumulated noradrenaline in the artery.

The release of noradrenaline was also examined by others (Häggendal et al., 1972a) who found that phenoxybenzamine increased the release of noradrenaline in response to nerve stimulation in rat MPV. Similar results were obtained in the rabbit MPV by Hughes (1972). He used field stimulation, measured noradrenaline output by bioassay, and found that release was proportional to rate of stimulation and that noradrenaline output was increased, then decreased, by cocaine but was only increased by phenoxybenzamine or corticosterone.

The source of noradrenaline (stored versus newly synthesised) released during stimulation was studied by Hughes and Roth (1974). They found that the output of newly synthesised noradrenaline per stimulus pulse was constant but that of stored noradrenaline was increased as the duration of the stimulus increased. Using similar techniques Greenberg (1974; 1975a) demonstrated that exogenous prostaglandin E_2 decreased, whereas inhibition of prostaglandin synthesis preferentially promoted, the release of newly synthesised noradrenaline.

The release of prostaglandin by noradrenaline also has been studied in rabbit MPV (Simmet and Hertting, 1980), and it was found that potassium- but not noradrenaline-induced contractures were accompanied by prostaglandin release.

The interaction between field stimulation and exogenous noradrenaline was examined by Ljung and Wennergren (1972). They found that the former had an effect up to 10^{-5} M of added noradrenaline. This was interpreted to indicate that local concentrations of released noradrenaline exceeded 10^{-5} M which was similar to the values calculated previously (Ljung, 1969). Other investigators (Bevan and Su, 1974) using different techniques calculated the concentration of noradrenaline in the synaptic cleft to be 6×10^{-9} M in rat MPV compared to 7×10^{-7} M in rabbit pulmonary artery.

The putative role of β-adrenoceptors in modulating the release of noradrenaline from nerves also has been studied. Dahlöf et al. (1978) found that the presence of noradrenaline or adrenaline increased the release of noradrenaline in response to nerve stimulation and that this increase was inhibited by propranolol in the rat MPV. They suggested that there was a β-adrenoceptor-mediated positive feedback system which operated presynaptically whereby noradrenaline could facilitate its own release in the rat MPV. These conclusions were supported by the observations that propranolol or butoxamine blocked the increase in release that isoprenaline produced (Westfall et al., 1979). Furthermore, the effect seems to be mediated via β_2-adrenoceptors because practolol, a somewhat selective β_1-adrenoceptor antagonist, did not inhibit the effects of isoprenaline. Similar findings were made using metoprolol as the selective β_1-antagonist (Dahlöf et al., 1980).

Yohimbine also enhances noradrenaline release produced by transmural stimulation (Török et al., 1985) which suggests that α_2-adrenoceptors are involved in the inhibition of noradrenaline release via a negative feedback system. Similar effects of yohimbine on release of noradrenaline from the MPV of the rat in vivo also have been reported (Remie and Zaagsma, 1986). Estrogen also has been reported to inhibit potassium-induced release of noradrenaline (Bengtsson, 1978) and ATP has been reported to inhibit release of noradrenaline in response to transmural stimulation in the rat MPV (Moylan and Westfall, 1979). Similarly, opioid agonists selective for κ- or δ-, but not μ-, receptors have been shown to inhibit the release of noradrenaline from transmurally stimulated rabbit MPV. Naloxone antagonised the inhibitory effects of the opioid agonists (Szabo et al., 1987). Thus, adrenoceptors are not the only modulators of release of noradrenaline from nerve endings.

The effect of transmural stimulation on perfused dog MPV and the interaction of this preparation with reserpine, guanethidine, and atropine also have been reported (Hall and O'Connor, 1972). The dog MPV also was used by Vanhoutte (1974) who examined the effects of acetylcholine on transmural stimulation. He reported that acetylcholine decreased the radioactivity released by such stimulation in veins previously exposed to [^{3}H]noradrenaline but increased the contractile response. He concluded that acetylcholine decreased adrenergic transmission but also had direct contractile actions. Acetylcholine also inhibits the release of noradrenaline induced by potassium (Verbeuren and Vanhoutte, 1976). This was interpreted (incorrectly as it turns out) as evidence that vasodilation induced by acetylcholine is due to its action on sympathetic nerves.

B. Cholinergic, Serotonergic, and Histaminergic Innervation

The cholinergic innervation of the rat MPV has been studied histochemically using cholinesterase staining (De Luca et al., 1982). Positively staining fibres were seen in an adventitial plexus and between media and adventitia. The staining was still present after 6-hydroxydopamine treatment in vivo. Cholinergically mediated constriction also has been demonstrated in the dog MPV in situ (Uematsu et al., 1984) and in vitro (Yoshioka et al., 1988a). The functional significance of this innervation is unknown.

Immunohistochemistry also has shown serotonin in the adventitia of rat MPV (Barja et al., 1986), but neither depletion of serotonin by treatment with the mast cell degranulator, compound 48/80, nor attempts to antagonise the actions of serotonin by treatment with antibody was able to alter spontaneous activity in the vein. Therefore, the function of the serotonin is unknown.

Treatment of ring preparations of rat MPV with nisoxetine or fluoxetine (amine uptake inhibitors) potentiated responses to applied noradrenaline but not to

serotonin (Cohen and Wiley, 1977b). This was interpreted to indicate that uptake of serotonin does not play a role in terminating the action of serotonin. Recently, it has been reported that treatment with 6-hydroxydopamine depletes the tissue of serotonin as well as noradrenaline, and it is suggested that the two amines are cotransmitters in the sympathetic nerves to the mesenteric vasculature in the rat (Gale and Cowan, 1988).

Histamine also has been found using biochemical techniques in the wall of the MPV (Howland and Spector, 1972; El-Ackad and Brody, 1975) but no mast cells were identified in MPV from rats, cats, dogs, or sheep, even though histamine was present. Mast cells were identified only in MPV from cows (El-Ackad and Brody, 1975). It seems that histamine can be synthesised by non-mast cells in the MPV of most species.

C. Nonadrenergic, Noncholinergic Neurotransmitters

The presence of nonadrenergic, noncholinergic nerves was first suggested by experiments using rabbit MPV (Hughes and Vane, 1967; 1970) when it was observed that transmural stimulation at 0.2–1 Hz produced a long-lasting relaxation which was antagonised by tetrodotoxin, but not by phenoxybenzamine, and which could be mimicked by nicotine. This work has been followed up primarily by Burnstock and his colleagues (1979) who used histochemical and pharmacological techniques to compare rabbit and guinea pig MPV regarding the effects and content of ATP. In keeping with the earlier observations of Su (1975, 1978) on rat MPV, ATP was found to relax the rabbit MPV but to contract the guinea pig vessel. These effects paralleled the finding of quinacrine-positive cells (indicating the presence of ATP) in rabbit but not in guinea pig MPV. ATP seems to relax the MPV from those species in which it normally occurs but to contract the MPV of species in which ATP cannot be demonstrated. Quinacrine-positive cells similarly are reported to be absent from rat MPV (Cantagalli et al., 1983). Subsequent work has confirmed the differences in the ATP content of rat, guinea pig, and cat MPV (Burnstock et al., 1984).

Recently, it was reported (Kennedy and Burnstock, 1986) that at 25°C ATP potentiates contractions induced by noradrenaline in the MPV of guinea pig and rat. This may indicate a species-dependent effect of ATP, or a temperature-dependent one. It should be noted that others (Sjöberg and Wahlström, 1975) have reported that ATP has only initial excitatory activity followed by inhibition even in rat MPV. Thus, the effects of ATP are not straight forward.

The effects of adenosine on release of noradrenaline in response to transmural stimulation have been studied in the rat MPV (Enero, 1981) and were reported to be inhibitory, although a dose-response relationship was not demonstrated. The release of purines and of noradrenaline during transmural electrical stimulation also has been studied (Levitt and Westfall, 1982). It was found that both are released by nerve stimulation but the amount of purine released was reduced by 20%, whereas noradrenaline was not reduced by the α-adrenoceptor antagonist prazosin. The latter blocked mechanical response to nerve stimulation, however. These observations were taken to indicate that 80% of the purines were released from neurons in the rat MPV. Treatment of the tissue with 6-hydroxydopamine in vitro reduced the release of purines by 50% which is consistent with only part of the purines being released from nerves.

D. Peptidergic Innervation

VIP was demonstrated by immunohistochemistry in nerves of the rat MPV in 1982 (Järhult et al., 1982). Exogenous VIP was found to relax the vein and nerve stimulation released VIP into the bathing medium but did not relax the tissue unless there was adrenergic activation of the tissue. These workers suggested that VIP plays a role in the regulation of portal blood flow.

VIP has been reported to be localised to nerves in the adventitia (Barja and Mathison, 1982), whereas substance P is reported to be in the adventitial and the medial plexuses along with adrenergic nerves. On the other hand, VIP also has been identified in both adventitial and medial plexuses (Ishii and Shimo, 1983). VIP has been reported to be released into the perfusate when the rabbit MPV is electrically stimulated in the presence of adrenergic and cholinergic blockade (Hellstrand et al., 1985). This release was accompanied by relaxation of the vein. VIP stimulates cyclic AMP production in membrane particles of rat MPV and it has been suggested that the relaxation that VIP can induce is related to increased cyclic AMP (Amenta et al., 1988).

Substance P has been implicated in afferent transmission from the MPV. Stoppini et al. (1984) observed that in vivo treatment of rats with capsaicin markedly depleted the substance P content of the vein as measured histochemically. Such treatment inhibited the response of the hypothalamus (determined electrically and by measurement of vasopressin release) to bradykinin perfusion of the vein but not to perfusion with hypertonic saline. The cell bodies of the nerves containing substance P have been traced to spinal sensory ganglia in the rat (Barja and Mathison, 1984).

Calcitonin gene-related peptide has been identified by immunohistochemistry in the MPV and in dorsal spinal ganglia of the rat; therefore, it also has been suggested that this peptide is involved in afferent neurotransmission (Sasaki et al., 1986).

E. Reinnervation and Ontogeny

The reestablishment of functional innervation has been studied after homologous transplantation of the MPV to the caudal diencephalon accompanied by extirpation of the cervical sympathetic ganglia (Bjorklund et al., 1975). After removal 25–30 days later the vessels

responded to transmural stimulation, thus demonstrating the regeneration of central nerve endings.

The ontogeny of postnatal innervation of the MPV has been studied in the rat (Ljung et al., 1975b) and in the rabbit, cat, and guinea pig (McMurphy and Ljung, 1978). In the rat, spontaneous contractility appeared during the third postnatal week and responses to transmural stimulation appeared at the end of the first week, whereas responses to noradrenaline or acetylcholine appeared early in the first week. Thus, functional innervation did not precisely parallel response to agonists, presumably because receptors and neurons develop at different rates. In the cat and guinea pig responses of the MPV of the newborn were the same as those of the adult. The development of responses of the rabbit MPV was more rapid than in the rat but not as rapid as in the cat and guinea pig. These workers concluded that the development of responses was controlled by a genetically predetermined schedule.

Ljung and coworkers (Lundberg et al., 1976) also studied the postnatal development of adrenergic innervation histochemically. They observed that the adrenergic nerves in the rat grew centripetally from the external plexus during the first 3 weeks after birth with the adult pattern of innervation being established by 5 weeks.

The density of adrenergic innervation of the MPV of the rat also has been compared with the innervation of cerebral vessels. The density as measured visually using the formaldehyde fluorescent technique was higher in the MPV (Rosenblum and Chen, 1976).

Burnstock's group (Crowe and Burnstock, 1982) also has used fluorescent histochemistry on the MPV to describe the ontogeny of its innervation. They found that small intensely fluorescent cells were predominant in rabbit portal vein at 25 days' gestation but these cells began to disappear at 31 days. In adult veins adrenergic nerves were predominant. Not everyone agrees with the proportion of ATP-containing neurons reported by Burnstock who estimated a ratio of 1:7 ATP to noradrenaline. Gibbins (1981) found the proportion to be 50:50, but ATP certainly is present and most likely is a transmitter in the rabbit MPV.

Ljung and colleagues (1979) examined the effects of 6-hydroxydopamine given to newborn rats. They found that this agent prevented the development of adrenergic nerves, as judged by histochemistry and the presence of supersensitivity to noradrenaline, but did not interfere with the normal development of the two muscle layers in the MPV. They concluded that adrenergic innervation does not have trophic actions that are manifest by structural effects on vascular muscle.

The ability of 6-hydroxydopamine to denervate the MPV in vitro was demonstrated using rat veins. Functional denervation and supersensitivity (Aprigliano and Hermsmeyer, 1976) as well as loss of catecholamine fluorescence were observed (Aprigliano et al., 1976) after treatment with 6-hydroxydopamine. This same group (Aprigliano and Hermsmeyer, 1977) administered 6-hydroxydopamine to rats in vivo and produced partial denervation as indicated by a reduced response to nerve stimulation, reduced uptake of noradrenaline, and reduced catecholamine fluorescence. They measured increased responses to both noradrenaline and barium as well as partial depolarisation of the smooth muscle cells and concluded that the loss of adrenergic innervation produced postjunctional effects. This group later reported that rat MPV maintained in tissue culture for 2 days showed supersensitivity to noradrenaline and to barium as well as an increased rate of relaxation after the barium contracture (Abel et al., 1980). The contractile supersensitivity, but not the alteration of relaxation, could be prevented by exposure of the tissue to noradrenaline.

A comparison of the effects of 6-hydroxydopamine, reserpine, and cocaine on the responses to a variety of stimulants has been done on the MPV of rat, rabbit, and guinea pig (Kaiman and Shibata, 1978a). The results are difficult to interpret, but all three agents increased the responses to noradrenaline but did not uniformly increase responses to barium or potassium. The authors correlated the changes in responsiveness with changes in $^{45}Ca^{2+}$ efflux. Species variation in responses also were observed because the rat veins were not affected by reserpine in contrast to veins from cat and guinea pig. Reserpine similarly was found to increase the amplitude of spontaneous contractions of MPV from cat and guinea pig but not from rat (Kaiman and Shibata, 1978b). Species variations also have been found in the interaction of 6-hydroxydopamine with cocaine. The former abolished the ability of cocaine to potentiate noradrenaline-induced contraction in guinea pig, but not rabbit, MPV (O'Connor and Slater, 1981b).

F. Summary

The MPV of all species examined is adrenergically innervated. Serotonin may be linked to adrenergic transmission in the rat. Many species have cholinergic innervation as well. Histamine is present in the MPV but not in mast cells, except in the bovine MPV. Peptidergic nerves are present and some of the peptides may be involved in afferent (sensory) innervation. The effect of exogenous purines such as ATP and the presence of purinergic nerves is species dependent. Responses to agonists appear earlier postnatally in the MPV in cat and guinea pig than in rat and rabbit and their appearance is independent of innervation. 6-Hydroxydopamine produces loss of adrenergic, and to a lesser extent, purinergic nerves in the MPV both in vivo and in vitro.

IV. Electrical Events

A. Action Potentials

The first recordings of electrical activity in the MPV of rabbit were made using a sucrose-gap electrode (Cuth-

bert and Sutter, 1964) and in the MPV of rat using intracellular microelectrodes (Funaki and Bohr, 1964). Both groups observed bursts of action potentials coincident with the spontaneous contractions characteristic of this vein. The spontaneous contractions occurred at a frequency of 3–6/min. Both groups also reported that the frequency of electrical spiking increased when a contracture of the vein was induced by noradrenaline. These were the first reports of action potentials in a mammalian vein.

The relationship between spike frequency and changes in tension produced by several drugs then were examined in longitudinal strips of rabbit MPV (Cuthbert and Sutter, 1965). It was found that there was a good correlation between frequency and tension when either noradrenaline or angiotensin were applied but that firing rates soon decreases while tension was sustained or even increased during continued application of the drug. There was an initial correlation but later a dissociation between frequency of action potentials and tension presumably because both voltage- and receptor-operated ion channels were activated by applied agonists. Increased ionic conductance through either or both types of channel would result in contraction. It is not clear whether time of exposure to or concentration of agonist is the chief determinant as to which type of channel is activated. In this paper evidence was also presented that reduction of the concentration of calcium in the superfusate altered the configuration of the action potentials.

B. Membrane Potential

The effect of ouabain on action potentials and resting membrane potential was examined and it was found that treatment of rabbit MPV with 10^{-5} M ouabain produced increased frequency of action potentials accompanied by contraction, which was followed by electrical quiescence and depolarisation as determined by intracellular recordings (Matthews and Sutter, 1967). This was consistent with the resting membrane potential being due to a potassium potential because tissue potassium was reduced and tissue sodium increased during depolarisation. Similar effects of ouabain were seen in the sheep MPV, and in addition, tetrodotoxin was found not to affect the spontaneous electrical or contractile activity of that vein (Holman and McLean, 1967). Taken together these observations confirmed that the action potentials were myogenic.

A series of papers then appeared from Johansson and colleagues (1967) who used the rat MPV and sucrose-gap electrode for their studies. They too observed that noradrenaline increased action potential frequency and tension but found that a dissociation between the two also could be seen. They examined the effects of alteration of ionic composition and found that increasing extracellular potassium depolarised the membrane, whereas increasing calcium hyperpolarised it. Decreasing extracellular calcium decreased action potential frequency (Axelsson et al., 1967). The rat and rabbit MPV thus were found to have similar electrical characteristics and similar findings were soon reported for sheep (Holman and McLean, 1967).

The term pharmacomechanical coupling was coined by the Somlyos (Somlyo and Somlyo, 1968) to describe the ability of agonists such as noradrenaline to induce a contracture in the absence of demonstrable electrical changes or under circumstances when electrical activity was almost certain to be absent. They too observed a lack of correlation between tension and action potential frequency during exposure of rabbit MPV to noradrenaline.

C. Excitation

The electrical correlates of spontaneous contractility have been examined. Hyperosmolarity of extracellular fluid produced by addition of sucrose was able to desynchronise the spread of electrical excitation in the rat MPV (Johansson and Ljung, 1967), presumably by interfering with cell to cell transmission. Using multiple pressure electrodes Ljung and Stage (1970) found that there appear to be multiple pacemakers in the rat MPV. These observations were later confirmed (Hermsmeyer, 1973).

Intracellular recording showed the guinea pig MPV also to have spontaneous contractions accompanied by bursts of action potentials (Golenhofen and von Loh, 1970). A resting membrane potential of −40 to −50 mV is present (Kuriyama et al., 1971). The depolarisation produced by a 10-fold increase in extracellular potassium has been found to be approximately 40 mV (Kuriyama and Suzuki, 1978). Conduction velocity initially was reported to be slower in guinea pig than in rat MPV (Ito and Kuriyama, 1971) but later was corrected to a value of 0.97 cm/s. It also has been observed during measurement of action potentials with intracellular electrodes in the MPV of guinea pig, rabbit, and sheep that only small areas of tissue contracted spontaneously. It was concluded that conduction is poor in these tissues (Hermsmeyer, 1971). It should be noted, however, that spiral strips of these veins were used in these latter experiments. The muscles of the MPV are oriented longitudinally and, therefore, conduction might have been disrupted in the experimental tissues. Conduction in rabbit MPV has been compared with the aorta and propagation has been demonstrated to occur in the former but not in the latter (Bevan and Ljung, 1974).

Stretch of the MPV increases the rate of action potential discharge (Cuthbert et al., 1964) and the more rapid the stretch the more effective is the stimulus (Johansson and Mellander, 1975). This myogenic response could be involved in autoregulation.

Spontaneous action potential frequency is reduced in rat MPV by hypoxia but not much affected by lack of glucose in the bathing solution (Hellstrand et al., 1977). Vibration, which causes loss of tension, does not alter

spontaneous action potentials (Sjöqvist and Ljung, 1980).

The MPV also has been used as a source of endothelial cells (Northover, 1975). A membrane potential of approximately −40 mV is present which could be reduced by addition of potassium or histamine.

D. Summary

Microelectrode and sucrose-gap studies have shown that the MPV of all species examined has a resting membrane potential of −40 to −50 mV and spontaneous action potentials are accompanied by contractions, the frequency of which normally is about 3/min. Excitant drugs increase the frequency of action potentials concomitant with an increase in tension but pharmacomechanical coupling also can occur. The resting membrane potential is consistent with a potassium or chloride potential. The frequency and configuration of action potentials are altered by reducing external calcium. The spontaneous contractility seems due to the presence of multiple pacemakers in the MPV. The ions and ion channels involved in the various phases of electrical events will be discussed in the next section.

V. Ions and Ion Channels

A. Calcium

The roles of calcium ions in membrane and action potentials and in E-C coupling have been persistent themes of studies involving the MPV. It was observed quite early that the absence of calcium added to the bathing fluid resulted in loss of spontaneous contractility and decreased rate of firing of action potentials as well as loss of the contractile effect of agonists such as noradrenaline in the rabbit MPV (Cuthbert and Sutter, 1965). Similar findings were made using sucrose-gap electrode recordings from rat MPV (Axelsson et al., 1967). Reduction of external calcium also was reported to alter the length-tension curves of cat MPV in response to noradrenaline (Alexander, 1967b).

There is an optimum concentration of calcium that will sustain action potentials. The frequency of firing is reduced at concentrations of external calcium >10 mM and <0.5 mM (Biamino and Johansson, 1970). It has been suggested that there are several pools of calcium involved in contraction (Greenberg et al., 1973b). This was the interpretation of experiments on dog MPV in which ruthenium red was reported to antagonise contractures to barium or potassium but not to noradrenaline. These experiments are difficult to assess, however, because the dose-response curves do not show maximum responses. Based on responses to potassium after varying times in calcium-free bath fluid it has been suggested that there is a superficial bound pool of calcium in the rat MPV that cannot, by itself, support contraction but is released by external calcium (Sigurdsson et al., 1975).

The rat MPV clearly is much more dependent on external calcium than is rat aorta (Sutter, 1976) because the former loses its ability to respond to agonists when calcium is not added to the external fluid, whereas the aorta requires the use of calcium chelators to achieve the same loss of responsiveness.

The addition of calcium to the bathing fluid does not cause a contraction of the MPV unless the vein is depolarised by increased extracellular potassium (Hellstrand et al., 1972) or has been pretreated with a calcium chelator (Collins et al., 1972a). Presumably this is because ordinarily calcium permeability is low but depolarisation or removal of calcium from membrane sites causes increased permeability. Barium, in contrast to calcium, can depolarise and initiate a contraction in rat MPV (Taranenko, 1974). There also is an interaction between agonists such as noradrenaline or angiotensin and calcium which is more than merely depolarisation (Mantel et al., 1975). These workers produced dose-response curves to calcium in the presence of 106 mM potassium with and without the addition of noradrenaline or angiotensin. They observed that the latter two agonists shifted the calcium dose-response curve to the left. This would seem to be a good functional demonstration of the existence of receptor-operated calcium channels in the rat MPV. Similarly, the ED_{50} for calcium in the presence of potassium is 2.9×10^{-3} M, whereas in the presence of adrenaline it is 7×10^{-4} M (Savino and Taquini, 1977), which is consistent with the existence of both voltage- and receptor-operated calcium channels. When binding studies are done using dihydropyridine-type calcium antagonists, the binding characteristics of membranes from horse or rat MPV are very similar (Dacquet et al., 1989) and are characteristic of both voltage- and receptor-operated channels.

The use of $^{45}Ca^{2+}$ has been widespread, but it seems doubtful that it has contributed much to our understanding of calcium handling. For instance, it has been reported that prostaglandins E_1 and E_2 decrease tone, whereas prostaglandins A_2 and B_2 increase tone, but $^{45}Ca^{2+}$ flux is reduced by all of them in dog MPV (Greenberg et al., 1973c). Similarly, after treatment with hydrochlorothiazide, rabbit MPV took up more $^{45}Ca^{2+}$, had double the residual calcium, and had similar $^{45}Ca^{2+}$ efflux compared to controls (Zsotèr and Suffiad, 1973). The effects of cold storage on $^{45}Ca^{2+}$ efflux and on responses to potassium, methoxamine, and barium have been compared in rat, rabbit, and guinea pig MPV (Kaiman and Shibata, 1978b). Cold storage increased $^{45}Ca^{2+}$ efflux in all three veins but had variable effects on responses to the contractile stimuli. There thus is a lack of correlation between the measurements of $^{45}Ca^{2+}$ flux and contraction under a variety of conditions. Possible reasons include the time scale on which most flux studies are made compared to the seconds during which contraction is initiated, the complex kinetics of calcium movements, and the possible compartmentalisation of that calcium

involved in initiating contraction. We still lack kmowledge of the sources, sinks, and non-steady state kinetics of that calcium that activates the contractile machinery.

B. Potassium

The role of potassium was investigated indirectly by measuring this ion, sodium ion, and intracellular membrane potentials in rabbit MPV treated with ouabain. Potassium was found to be markedly reduced and sodium to be increased when the membrane was depolarised (Matthews and Sutter, 1967). The effects of altering external potassium also were studied in rat MPV using a sucrose-gap apparatus (Axelsson et al., 1967). Reduction of external potassium was found to hyperpolarise the membrane and to reduce the frequency of spontaneous action potentials. Increasing external potassium was observed to reduce the resting membrane potential proportionally to the concentration of potassium.

The effects of sudden reduction of potassium as well as sodium or chloride also were examined and it was found that reduction of each gave a transient electrical and mechanical excitation. Restoration of the concentration of ion restored excitation to normal (Johansson and Jonsson, 1968b). Even when spike discharges are abolished by cooling, potassium produces a contracture proportional to its extracellular concentration (Uvelius and Johansson, 1974). Some of the contraction produced by elevation of external potassium can be due to release of noradrenaline from the vein (Bengtsson, 1977). Therefore, care must be taken to prevent adrenergic effects when studying the effects of increased external potassium. A comparison of the effects of elevated potassium on the mechanical activity of guinea pig uterus, taenia coli, and MPV has been done (Gabella, 1978). In contrast to taenia, the contractile response of the MPV to potassium is proportional from 5.5 to 120 mM. In the taenia, a maximum response is obtained at 20–25 mM. Much less fade of response in the continued presence of potassium was also seen in the MPV compared to taenia. There is no ready explanation for these apparent differences in the two tissues.

The permeability of the membranes of the rat MPV has been studied and it was calculated, using osmotic changes to nonelectrolytes as a criterion, that the average pore radius was 3.7 Å and that there were 103 pores per cell (Johansson, 1969; 1970). This was the first mention of ionic pores in the MPV. Using radioactive potassium, Jonsson (1971a) calculated the permeability to potassium to be 9.4×10^{-6} cm/s. Radioactive potassium and atomic absorption spectroscopy have been used to relate the intracellular concentration of potassium and sodium to the resting membrane potential (Wahlström, 1971). Wahlström found that the Nernst equilibrium potential for the calculated concentration of intracellular sodium would be +21 mV and for potassium −86 mV. Therefore, the observed resting membrane potential in the rat MPV of −40 to −50 mV is closer to the potassium equilibrium potential.

In a later paper Wahlström (1973a) reported that the ratios of permeabilities for potassium, sodium, and chloride were 1:0.034:0.86 and that the calculated membrane potential was −42 mV, whereas the measured membrane potential was −45 mV in rat MPV. It was concluded that potassium and chloride, therefore, contributed most to the resting membrane potential. Wahlström (1973b) also studied the effects of noradrenaline on the several permeabilities and found that permeability to potassium and chloride was increased by noradrenaline but not permeability to sodium.

The relationship of increases in permeability to potassium and contraction produced by noradrenaline has been examined in guinea pig MPV (Chen and Sunahara, 1972). Noradrenaline produced a dose-dependent increase in ^{86}Rb efflux and tension, both of which were antagonised by phentolamine. Removal of extracellular calcium prevented the increase in tension but did not reduce the increase in ^{86}Rb efflux produced by noradrenaline. This is consistent with calcium, and not rubidium (potassium), being responsible for coupling excitation to contraction, although permeability to both is altered by noradrenaline.

4-Aminopyridine increases the spontaneous contractility of the rat MPV. The effect was not blocked by propranolol or phenoxybenzamine or by surgical or chemical denervation, and the authors concluded that 4-aminopyridine blocks the transient potassium conductance that accompanies the action potential in this tissue (Leander et al., 1977). Similar conclusions were reached for guinea pig MPV; 4-aminopyridine and procaine both decrease potassium conductance (Hara et al., 1980).

C. Sodium

The effect of reducing extracellular sodium has been studied. Substitution of sodium bicarbonate with sodium-free Tris solution does not abolish the ability of the rat MPV to generate action potentials (Biamino and Johansson, 1970). Reduction of sodium was, however, found to slow the rate of relaxation in these same experiments. Replacement of sodium by sucrose or choline chloride in the cat MPV results in a contracture that is reduced in the absence of external calcium (Zafirov et al., 1983). This was interpreted to indicate that there is sodium-calcium exchange in the cat MPV.

There has been discussion of the effects of substitution of cations with Tris-containing buffer solutions. Altura and coworkers (Turlapaty et al., 1978) reported that Tris increased frequency and decreased amplitude of spontaneous contractions as well as decreased responses to agonists in rat MPV. They (Turlapaty et al., 1979b) later reported that Tris also altered calcium flux. The inhibitory effects of Tris on contractility were not confirmed by others (Johansson et al., 1979). Altura's group (Altura et al., 1980b) again suggested that certain buffers altered

the responses to agonists; contractions of rat MPV to prostaglandins were reduced by Tris, HEPES, or 4-morpholinepropanesulfonic acid at 5 mM concentration. This controversy was discussed by Karaki and coworkers (1981a) who found that use of Tris buffer did not inhibit spontaneous contractions or responses to agonists in rat MPV if the pH were maintained at 7.4. The same group (Karaki et al., 1981b) investigated the effects on contractile responses in the rat MPV of substitution of HEPES or 4-morpholinepropanesulfonic acid for sodium bicarbonate and found no effect of such substitution provided that the pH was kept constant. The same conclusion was reached by Sigurdsson (1983) concerning the importance of pH. When substituting for sodium with Tris or HEPES, pH is important.

The concentration of sodium in rat MPV cells has been estimated to be 13 mEq/litre (Båth et al., 1971) using atomic absorption spectroscopy and 167 mmol/kg dry weight as determined by electron probe analysis of rabbit MPV (Somlyo et al., 1979). The values for other ions are: K, 611; Cl, 278; Mg, 36; Ca, 1.9; and P, 247 mmol/kg dry weight. The relatively high value for chloride is particularly noteworthy. The value for intracellular sodium measured by electron probe analysis is twice the value calculated from lithium washout studies (Junker et al., 1984).

The flux of sodium as affected by ouabain and reduced calcium has been examined by electron probe analysis (Wasserman et al., 1986). It was observed that calcium-free solutions markedly inhibited ouabain-resistant sodium and chloride efflux which could be restored by 0.2 mM calcium. This suggests an interaction between sodium and calcium movements in the MPV. Results of further experiments in which the quantitative effects of calcium on sodium efflux were examined were consistent with that view and it was also suggested that calcium had to reach intracellular sites for the increased sodium efflux to be seen (Kaplan et al., 1987). It also has been suggested based on sodium-loading experiments that a sodium-calcium exchange can operate in mitochondria (Broderick and Somlyo, 1987).

D. Other Cations

Manganese which antagonises calcium in rabbit MPV (Collins et al., 1972b) also can gain access to ethyleneglycol bis(β-aminoethyl ether)-N,N,N′,N′-tetraacetic acid-resistant sites (presumably intracellular) in rat MPV (Sutter et al., 1988). After it reaches these sites the magnitude of responses to noradrenaline or potassium are gradually restored to normal or greater than normal. The rate of contraction also is slowed by manganese in the bathing fluid and this seems to be an extracellular effect. Thus, manganese has inhibitory effects on contraction only when it is extracellular. Although other cations (Mg^{2+}, Ni^{2+}, Co^{2+}, Sr^{2+}, Cd^{2+}, La^{3+}, Sn^{2+}) can inhibit contractile responses to noradrenaline, potassium, or barium, manganese is unique in being able also to increase the responses to these agonists. Manganese also inhibits spontaneous electrical and mechanical activity in guinea pig MPV (Nanjo, 1984). In this preparation, too, manganese seems to have intracellular effects in that low concentrations of manganese can increase the response to caffeine.

Strontium which often has been used to substitute for calcium has been shown by electron microscopy to enter the S-R and mitochondria of rabbit MPV (Somlyo and Somlyo, 1971). Strontium or barium can partially substitute for calcium in rat MPV (Uvelius et al., 1974; Uchida, 1975) in that the former supports spike activity, whereas the latter supports contractions. Strontium seems to be able to support potassium-induced contractures but not those induced by noradrenaline (Arner et al., 1983). Perhaps strontium passes through voltage-dependent channels more readily than through receptor-operated ones.

There is evidence that barium initiates contractions in part by decreasing potassium conductance (Hermsmeyer, 1976). Hermsmeyer observed that barium produced an increase in input resistance and depolarisation as well as a decrease in the slope of the curve relating resting membrane potential to the concentration of external potassium in the rat MPV and interpreted this to indicate that barium decreased potassium conductance. Subsequent investigations have confirmed the ability of barium to depolarise the rat MPV (Takata, 1979) and to increase electrical spike activity in a manner different from calcium (Uvelius and Sigurdsson, 1981). Barium contracts rat MPV in the absence of added external calcium (Sutter et al., 1988).

The effects of magnesium also are complex. It has been reported that the presence of 1.2 mM magnesium decreases the amplitude of spontaneous contractions in the rabbit MPV but also shifts the ED_{50} for calcium from 2.3 to 1.6 mM in the depolarised vein (Turlapaty and Carrier, 1973). The absence of magnesium in the bath fluid increases spontaneous activity in rat MPV, whereas spontaneous contractile and electrical activity is progressively depressed as magnesium concentration is increased to 10 mM (Sigurdsson and Uvelius, 1977). Increasing external potassium from 5 to 12 mM negated the effect of 10 mM magnesium and this was interpreted to mean that a high concentration of magnesium hyperpolarised the membrane. These investigators reported that magnesium was inhibitory to potassium-induced contractures only when the external concentration of calcium was 0.5 mM or less. On the other hand, we (Sutter et al., 1988) have found magnesium (8 mM) to be only inhibitory to the contractile effects of noradrenaline or potassium (80 mM) in the rat MPV in the presence of 2.5 mM external calcium. The reasons for this discrepancy may be that we waited until a maximum effect of magnesium had occurred.

Treatment of rat MPV with lanthanum (0.3 mM)

results in permanent inhibition of spontaneous contractions (Savino and Taquini, 1977). Slightly higher concentrations of lanthanum (0.5 mM) irreversibly inhibit both spontaneous and noradrenaline- or potassium-induced contractions (Sutter et al., 1988). Because lanthanum cannot be demonstrated to go intracellularly in MPV using electron microscopic techniques (Ebeigbe, 1984), most of its effects would seem to be extracellular.

Copper can inhibit spontaneous activity of rat MPV as well as human Fallopian tube (Larsson et al., 1976). Perhaps this is because the mechanisms involved in spontaneous contractility are similar in these smooth muscles. Nickel (1–10 μM) is inhibitory to spontaneous contractility and to the effects of transmural nerve stimulation in rat MPV (Rubányi and Inovay, 1982). At higher concentrations nickel also inhibits noradrenaline- and potassium-induced contractions in this tissue (Sutter et al., 1988).

E. Anions

As mentioned earlier, chloride was found to permeate the membrane of rat MPV almost as readily as potassium and permeability to both potassium and chloride was increased by noradrenaline (Wahlström, 1973a; 1973b). Other anions were examined for their effects on spontaneous contractions and it was found that nitrate and bromide ions increased, whereas pyruvate, isethionate, and benzenesulphonate decreased, spontaneous contractility (Wahlström and Svennerholm, 1974). The response to noradrenaline was shifted to the left by nitrate and bromide and was inversely proportional to the concentration of external chloride. Noradrenaline has been observed to produce an increase in membrane conductance with a depolarisation equilibrium potential of −2 mV in cells dissociated from rabbit MPV (Byrne and Large, 1988). This is consistent with an increase in chloride conductance produced by noradrenaline, an interpretation that is supported by recent observations on cultured cells of rat MPV using patch clamp techniques (Pacaud et al., 1989).

The effects of sodium vanadate on rat MPV have been examined and it has been found that vanadate increases spontaneous spike frequency and height of the accompanying contraction with no increase in basal tone (Shimamura and Sunano, 1988). The authors of this report argue that the effects of vanadate are different from reduced potassium or ouabain because neither of these agents blocked the vanadate effect. Further work is needed to quantify these observations.

F. Ion Channels

The patch clamp technique has been applied to the MPV. Rabbit MPV was used by Inoue et al. (1985) as a source of dispersed single cells after treatment with collagenase and trypsin. They observed two different ionic currents (termed KL and KS), the conductance of which depended on the potassium concentration and which were abolished by replacement of potassium by sodium or Tris. Both were sensitive to the concentration of calcium but only one (KL) was altered by tetraethylammonium. They suggest that these are potassium channels that play a role in repolarising the membrane after an action potential. The same group (Inoue et al., 1986) subsequently reported that a third channel (KM) is present that is less sensitive to the concentration of intracellular calcium than to extracellular calcium and is more sensitive to tetraethylammonium applied to the inner aspect of the membrane. Thus, three potassium channels have been reported but it remains to be seen whether they are truly different and how universally they are present in cells of veins from different species.

Using a whole cell voltage clamp technique, Ohya et al. (1988a) observed that calcium or barium currents were turned off by increasing intracellular calcium in dispersed cells of rabbit MPV. This was interpreted to indicate that a Ca-dependent inactivation of calcium currents exists in these cells. Recently, Imaizumi et al. (1989) reported a noninactivating calcium current present in cells dispersed from rabbit MPV. The relationship between these calcium currents remains to be defined. The calcium antagonist gallopamil (D600) seems to act from the outside of the cell. The evidence for this is that, when studied on cells isolated from the rabbit MPV by means of whole-cell voltage clamp technique, gallopamil inhibited the calcium current only when applied to the outside of the cell. Intracellular perfusion with gallopamil did not reduce the calcium current (Ohya et al., 1987).

As mentioned previously a chloride channel activated by noradrenaline has been detected using patch clamp techniques (Pacaud et al., 1989).

The relationship of protein kinase C to calcium channels has been explored using phorbol esters in rat MPV (Spedding, 1987). Phorbol-12,13-dibutyrate increased spontaneous activity in this tissue but did not induce contraction. Spedding concluded that protein kinase C was not directly linked to calcium channels.

G. Summary

External calcium concentration is very important for maintenance of both contractility and action potentials in the MPV. There are both voltage- and receptor-regulated calcium channels in this tissue. The membrane potential and ion permeabilities are consistent with an equilibrium potential close to potassium and chloride. The role of sodium in electrical events is minimal but a calcium-sodium exchange system seems to be present in the MPV. Strontium and barium can partially substitute for calcium, but other divalent cations are inhibitory, presumably because they compete with calcium at external sites. Manganese is special in that it is inhibitory when outside the cell but when it has moved into the cell manganese can increase maximum response. Calcium, potassium, and chloride channels have been detected with patch clamp techniques in cells dispersed from the

MPV. More than one calcium or potassium channel seems to be present.

VI. Excitation-Contraction Coupling

A. Membrane Electrical Events

As mentioned previously, an early question in vascular physiology and pharmacology was the role of membrane electrical events in initiation of contraction. The MPV provided an opportunity to investigate this problem because it possessed action potentials and their relation to contraction could be examined. With regard to noradrenaline, angiotensin, and histamine, all of which caused contraction of rabbit MPV, Cuthbert and Sutter (1965) found that tension was proportional to spike frequency and that both were increased in proportion to dose of agonist. It also was observed that the proportionality between action potential frequency and tension was lacking at higher doses of drugs, particularly noradrenaline, and also late in the effects of an agonist. The answer to the question of the relationship of spike frequency to tension was "yes, but not always." Johansson et al. (1967) demonstrated that rat MPV behaved similarly insofar as electrical and contractile responses to noradrenaline were concerned. These workers also reported that the MPV could contract in response to noradrenaline even during exposure to depolarising concentrations of potassium.

The term pharmacomechanical coupling was coined to describe the ability of agonists to contract smooth muscles in the absence of observable electrical events (Somlyo and Somlyo, 1968). This group also compared E-C coupling in rabbit aorta, pulmonary artery, and MPV. Among these vessels only in the MPV were action potentials involved in the coupling of contraction to agonist-induced excitation (Somlyo et al., 1969).

B. Sources of Calcium

The marked inhibitory effect of removal of calcium on responses to agonists in the MPV was observed by several groups of investigators (see section V). It remained for Somlyo's group to relate E-C coupling to the ultrastructure of the tissue. They correlated the presence of action potentials to the small volume of S-R present in MPV and taenia (Devine et al., 1972) in contrast to aorta and pulmonary artery which had more S-R. Similarly, the aorta and pulmonary artery maintained their response in the absence of calcium added to the bathing fluid. This led the Somlyo group to suggest that the S-R was a probable source of internal calcium but the problem remained as to the relationship of those internal stores to external calcium which is essential for contraction in the MPV. Later studies in which electron probe microanalysis of calcium content was used demonstrated that calcium in the cytoplasm of the rabbit MPV was increased during contraction compared to relaxation (Bond et al., 1984b). It has been reported that much of the cell calcium is localised in S-R as determined using electron probe microanalysis with very small probes (Somlyo et al., 1985).

A problem with assigning a functional role to calcium released from the S-R is the failure of most investigators to find that more than a very limited number of contractions can be elicited in the MPV in nominally calcium-free bathing solutions; the internal calcium does not seem to recycle. The evidence that recycling could occur involved using lanthanum to attempt to prevent the efflux of calcium (Bond et al., 1984a). Bond et al. also cooled the tissue to 23°C and washed out the noradrenaline (which was the agonist) before the peak of the contraction was reached. Under these conditions repeated contractions to noradrenaline could be maintained in the absence of external calcium.

The effect of the calcium antagonists verapamil and gallopamil (D600) on responses of guinea pig MPV were examined by Golenhofen and Hermstein (1975). They found what they termed a "spike activation" mechanism linking noradrenaline to contraction which was blocked by verapamil and D600. They also found a "spike-free activation mechanism" which was not blocked by the calcium antagonists. Both systems were dependent on the presence of external calcium. They concluded that there were at least two systems for transmembrane calcium flux in this tissue. Their conclusion emphasises the complexity of the handling of calcium and the close coupling of the concentration of external calcium to contractile events in the MPV.

The necessity of external calcium to initiate and sustain contraction in the MPV has been reported for rabbit (Collins et al., 1972a) and for rat (Sigurdsson et al., 1975; Sutter, 1976; Feletou et al., 1986). Sigurdsson suggested that there was a superficially bound calcium that was released by external calcium to initiate contraction. Such a store has never been directly demonstrated but the problem remains that external calcium is tightly linked to contraction in an ill-understood way in the MPV. There has been demonstrated an effect of ryanodine, an agent that interacts with S-R in striated muscle, on contractions of rat MPV but only in the presence of reduced external calcium and high external potassium plus noradrenaline. In normal calcium, ryanodine has an effect on neither spontaneous nor noradrenaline-induced contractions (Ebeigbe, 1982). This suggests that under usual conditions the S-R plays little role as a source of calcium for contraction in the MPV.

The guinea pig MPV has been used as a saponin "skinned" preparation (Nanjo, 1984). Neither noradrenaline nor acetylcholine could contract the saponin-treated vein, but added calcium or caffeine did so. The minimum concentration of calcium required to produce a contraction was 10^{-7} M and it was concluded that the guinea pig MPV was similar to other visceral smooth muscles which are spontaneously active. Ryanodine had

no effect on inositol 1,4,5-triphosphate-induced contraction in skinned guinea pig MPV or on noradrenaline contractions in intact preparations (Iino et al., 1988).

C. Calcium Indicators

Calcium indicators have been used to study E-C coupling in the MPV. In the ferret MPV the time course and intensity of the light signal produced by aequorin differed depending on the contractile stimulus used (Morgan and Morgan, 1984a). Morgan and Morgan observed that after an electrical direct current pulse, the light signal increased before contraction and decreased while contraction was still increasing. With phenylephrine as the stimulus, the aequorin signal increased rapidly then decreased while tension was increasing but stayed above baseline during the period of contraction. When potassium was the stimulus, light and force increased together and in a parallel fashion up to 50–60 mM potassium. Light emission was then further increased by 90 mM potassium, whereas force was not. The ratio of force to light signal was always higher with phenylephrine than with potassium. In a subsequent paper (DeFeo and Morgan, 1985), ferret aorta and MPV were compared with respect to their calcium-force relationships. It was found that phenylephrine always shifted the calcium-force curve to the left. The authors conclude that phenylephrine increases the sensitivity to calcium by means of a second messenger.

The effect of vasodilators on aequorin luminescence also was studied (Morgan and Morgan, 1984b). Isoprenaline reduced calcium as detected by reduction of luminescence only at very high concentrations (10^{-4} M), whereas papaverine and forskolin caused relaxation and did not alter light emission. Light and force were reduced by nitroprusside or by reduction of extracellular calcium. These results were interpreted to indicate that reduction of intracellular calcium is not the only means of causing relaxation in ferret MPV.

Quin-2 and aequorin were compared as indicators of intracellular calcium in isolated cells and strips of ferret MPV (DeFeo and Morgan, 1986). Quin-2 caused a shift to the right of the dose-response curve for contraction probably because quin-2 buffers intracellular calcium. This was suggested because the level of calcium produced by increased extracellular potassium is less in the presence of quin-2 than it is with aequorin, although the same amount of resting calcium is shown by the two indicators.

Comparisons also have been made of fura-2 and chlortetracycline as calcium indicators in isolated cells of ferret MPV versus aequorin as the indicator in strips of ferret MPV (DeFeo et al., 1987). The localisation of calcium differs depending on the time of loading of the indicator with fura-2 showing a homogeneous distribution early but heterogeneous images later. Fura-2 also interfered with contraction after prolonged loading times. Caffeine altered the appearance of calcium images after prolonged loading but not after short periods. The signal from aequorin was not altered by caffeine but that of chlortetracycline was altered by caffeine. DeFeo et al. concluded that these results were compatible with the idea that chlortetracycline is localised in organelles, aequorin is only in the cytoplasm, and fura-2 can localise in both cytoplasm and organelles. Whatever the correct interpretation of these results is, it is clear that the several calcium indicators are functionally quite different from one another.

D. Non-Calcium Messengers

The role of intracellular messengers such as protein kinase C and inositol phosphate in E-C coupling in the MPV is still uncertain. The phorbol ester phorbol-12,13-dibutyrate has been reported to increase spontaneous activity in the rat and guinea pig MPV (Spedding, 1987). It did not produce contracture as in the aorta of the rat but produced a transient contraction of the MPV only at 1 μg/litre concentration. Spedding concluded that in the other tissues he examined (aorta and taenia caeci) it is unlikely that protein kinase C is directly linked to calcium channels. One wonders whether that holds for the MPV, however, because of the distinct effect of phorbol-12,13-dibutyrate on spontaneous contractility.

Using whole-cell voltage clamp on cells isolated from the rabbit MPV Ohya et al. (1988b) found an effect of inositol 1,4,5-triphosphate. They reported that inositol 1,4,5-triphosphate can increase the frequency of a calcium-dependent outward oscillatory current and render more negative the voltage at which this current could be detected. Outward oscillatory current was prevented by pretreatment with 3 mM caffeine. The authors suggested that inositol 1,4,5-triphosphate activates the outward oscillatory current by releasing calcium from storage sites.

E. Summary

The spontaneous contractions in the MPV seem to be initiated by action potentials, but contractions produced by agonists can occur without demonstrable electrical events. This is consistent with the view that both voltage- and receptor-linked calcium channels are present in this vessel. The occurrence of spontaneous or agonist-induced contractions requires external calcium to be present. Whatever is the final source of calcium that acts intracellularly to produce a contraction, that source is closely linked to the extracellular space. Special circumstances must pertain for demonstration of any role of the S-R in recycling calcium during the contraction-relaxation cycle. The role of the S-R in normal contraction is unclear. The use of calcium indicators and of electron probe microscopy has demonstrated that internal calcium increases during contraction of the MPV. The relationship between intensity of the light signal produced by calcium indicators and force of contraction is

less than straight forward. The involvement of phosphoinositol and protein kinase C in E-C coupling is uncertain, although each can be demonstrated to be altered during contraction and to produce a variety of effects under certain conditions.

VII. Contractile Machinery

A. Biophysics

The mechanics of contraction of the MPV have been examined by a number of investigators including Alexander (1967a; 1967b) who studied the effects of noradrenaline and calcium on length-tension curves in spiral strips of MPV from cats. At any given length tension was increased by both of these agents. The stiffness of the rat MPV was measured and found to be similar to that of other smooth muscles and less than that of skeletal or cardiac muscle (Peiper et al., 1978). This group (Klemt and Peiper, 1978) also suggested that the rate of development of contraction is a good estimate of rate of cross-bridge formation.

The capacitance of the rabbit MPV has recently been compared with the vena cava (Brown and Heistad, 1986). The MPV was found to have a much smaller elastic modulus and to be much more compliant than the vena cava but to be able to respond to noradrenaline over the range of distending pressures from 2 to 10 mm Hg.

The active state of the rat MPV has been studied during contractions produced in the presence and absence of an electrically active membrane (Johansson, 1973a). The relationship between force development and active state was the same in both cases. The biophysics of quick load change has been studied and it was found that there were three components to a step change in force applied to the rat MPV: an immediate passive elastic recoil, an isotonic velocity transient, and shortening of the contractile element (Johansson et al., 1978). The force-velocity relationship also has been studied in chemically skinned (Triton) rat MPV (Arner, 1983). Calcium or magnesium could induce contracture in this preparation but 15 mM magnesium was required and only a submaximal response was produced. The length-tension relationships were similar with either magnesium or calcium. Stiffness and tension transients have been studied in permeabilised (by glycerination) guinea pig MPV using laser-flash photolysis to increase the time resolution (Somlyo et al., 1988). In the absence of calcium, liberation of ATP into muscle in which rigor previously had been induced, caused relaxation but caused contraction of previously relaxed tissue. Their explanation was that "cross bridges can bear a negative tension."

An even more theoretical analysis has been made in guinea pig MPV whereby a power spectral analysis of frequency of spontaneous contraction revealed three maxima and in this regard the MPV was similar to taenia coli (Bäsar et al., 1974).

B. Physical Agents

Decreasing pH with ammonium chloride interfered with contractility (Alexander, 1969) of dog MPV. The effects of increased carbon dioxide initially were reported to be inconsistent in rat and cat MPV (Stamm, 1972); however, later experiments on rat MPV indicate that decreasing pH by altering carbon dioxide tension or bicarbonate concentration to produce a metabolic or respiratory acidosis results in decreased contractility (Knehr and Linke, 1980).

The effects of temperature have been studied and it was found that strips of dog MPV relaxed during cooling from 37° to 29°C and contracted during warming to 43°C (Vanhoutte and Lorenz, 1970). Warming increased spontaneous contractility and cooling had the opposite effect. When contracture was produced in rat MPV by tetanisation, the rate of tension development was decreased by decreasing the temperature from 37° to 23°C but the extent of contraction was independent of temperature (Peiper et al., 1975).

Vibration has been found to induce relaxation of the rat MPV (Ljung and Sivertsson, 1972). Both electrically stimulated and spontaneous contractions are inhibited at a frequency of 200 Hz. Vibration did not much affect passive force and it was suggested that vibration exerts a direct effect on actin-myosin cross-links (Ljung and Sivertsson, 1975). Detailed analysis of the rate of recovery after vibration-induced relaxation has led to a model that supports the view that the relaxation is due to interruption of cross-bridges (Klemt et al., 1981). Interestingly, vibration also relaxes the anterior byssus retractor muscle of *Mytilus edulis* but tension was not regained at the time of cessation of vibration in this muscle during the "catch" phase (Ljung and Hallgren, 1975). In the rat MPV, however, tension was regained at the time of cessation of vibration at any stage of a contraction. Vibration has been reported to have a positive chronotropic effect on the spontaneous contractions of dog MPV but to reduce the size of the contractions (Ohhashi et al., 1979). The chronotropy is dependent on the presence of extracellular calcium. Recording of the electrical activity of rat MPV indicates that longitudinal vibration which relaxes the vein dissociates electrical from contractile events (Sjöqvist and Ljung, 1980). It has been suggested that vibration can play a role in the pathophysiology of vascular disease (Sivertsson and Ljung, 1976).

The effects of stretch on electrical and mechanical responses have been studied in the MPV of rabbit (Cuthbert et al., 1964; Holman et al., 1968a) and in rat (Johansson and Mellander, 1975; Sigurdsson et al., 1977; Johansson, 1983). All these investigators have found that stretch increases both electrical and contractile activity. The rate of stretch is the chief determinant of response (Johansson, 1983). Presumably, the responsiveness of the MPV to stretch accounts for the observation that

the rate of spontaneous contractions is proportional to perfusing pressure when the rabbit MPV is perfused in vitro (Rhodes and Sutter, 1971b). In those same experiments it was observed that the magnitude of the spontaneous changes in pressure showed a biphasic response to increasing perfusion pressure, an increase followed by a decrease; a sort of "Frank-Starling curve." The MPV, therefore, seems to manifest autoregulation.

The effects of osmolarity are confusing. Increase of osmolarity has been reported to increase and then decrease spontaneous activity of the rat MPV (Johansson and Jonsson, 1968a) possibly because it alters cell volume and cell to cell conduction. This interpretation was questioned, however, when it was found that increased osmolarity due to 50 mM sucrose inhibited spontaneous activity during a 5-min period, whereas hyperosmolarity due to urea only stimulated spontaneous contractility (Arvill et al., 1969). It subsequently was observed that the permeabiltiy of the cells of the rat MPV to electrolytes was altered at the time of exposure to hyperosmolar nonelectrolytes (Jonsson, 1971a). This could account for the effects of osmolarity on electrical and contractile events. Other investigators have reported either that hyperosmolarity due to mannitol or sucrose only transiently decreases rate and amplitude of spontaneous contractions (McKinley et al., 1974) or that hypertonic sucrose increases force and frequency of spontaneous contractions (Takenaga et al., 1978). The reasons for the different effects of the various nonelectrolytes are not clear. It subsequently has been reported that the contracture induced by hypertonic sucrose does not require the presence of external calcium (Andersson et al., 1974). There also is a contraction that occurs when rat MPV has been exposed to hypertonic urea and is returned to normal physiological salt solutions (Jonsson et al., 1975). This contraction is increased by reducing the temperature. Both the sucrose and urea contractures are thus quite different from the ordinary. They also are different from contractions in hypertonic saline which remain dependent on extracellular calcium (Hellstrand and Arner, 1980) and which are metabolically similar to potassium-induced contractures (Arner and Hellstrand, 1980). It may well be that part of the reason for discrepant results has been the lack of standardisation of measurement of force and failure to control for the effects of time. These have been looked at more recently and it seems that both hypo- and hyperosmolarity exert transient effects; hypoosmolarity increases both electrical and contractile activity and hyperosmolarity decreases these functions but both effects are transient. Integrated force per spike ultimately is increased by prolonged hyperosmolarity and decreased by hypoosmolarity (Sigurdsson and Johansson, 1981).

C. Biochemistry

Dinitrophenol was used to study the effects of uncoupling oxidative phosphorylation in guinea pig MPV (Horn and Kunamoto, 1970). Dinitrophenol uncoupled contraction from electrical activity in that electrical spike frequency was increased but the accompanying contractions were suppressed. The membrane-resting potential was not altered.

The rates of oxygen consumption and lactic acid production have been studied in longitudinal strips of bovine MPV (Peterson and Paul, 1974). From these experiments it was calculated that aerobic glycolysis could account for 30% of the total metabolic energy. Measurement of phosphagen content of rat MPV revealed that PCr breaks down during the cycle of spontaneous contraction and relaxation but ATP, ADP, or AMP do not (Hellstrand and Paul, 1983). About 10% of the total energy usage in rat MPV is due to Na^+/K^+-ATPase activity (Hellstrand et al., 1984). Phosphorus-31 nuclear magnetic resonance has been used to measure intracellular phosphagen content and pH in rabbit MPV (Hellstrand and Vogel, 1985). The values obtained were similar to those seen with other techniques except for ADP and inorganic phosphate which were much lower. During a sustained contracture due to high potassium, PCr content decreased but ATP content remained constant. Intracellular pH was 7. The felodipine-induced (calcium antagonist) inhibition of spontaneous contractions is accompanied by decreased oxygen consumption and lactate production very similar to that seen in the absence of external calcium. There was no reduction in tissue ATP, ADP, AMP, or PCr accompanying relaxation (Arner and Boström, 1988).

Oxygen utilisation was measured in bovine MPV (Paul et al., 1974) and those measurements were used to attempt to describe the thermodynamics of the system. Oxygen consumption in the rat MPV is much higher than in tonic vessels (Hellstrand, 1977). There is disagreement as to whether or not contractions due to high potassium are accompanied by increased oxygen consumption: Hellstrand (1977) says yes, others say no (Ruiz et al., 1982). Ruiz et al. also report that noradrenaline increases oxygen usage in rat MPV by interacting with both α- and β-adrenoceptors.

Decrease of pO_2 in vitro has been found to reduce spontaneous electrical spiking and the accompanying contractions in rat MPV (Hellstrand et al., 1977). Noradrenaline- or potassium-induced contractions were reduced only at the extremes of hypoxia. In glucose-free media agonist-induced contractions were affected much more than spontaneous electrical or contractile events. By means of an oxygen electrode Hellstrand (1978; 1979) showed that pO_2 at the surface of the vein cycles during spontaneous contractions in vitro. The effects of hypoxia are antagonised by manoeuvres that substitute for calcium such as addition of barium or make calcium more available as by reduction of external sodium (Sigurdsson et al., 1981). These authors conclude that hypoxia has a membrane effect that reduces the ability of the mem-

brane to generate spikes and/or pacemakers. It subsequently has been suggested that hypoxia also can reduce contractility by a metabolic effect because, although ATP levels of the tissue are not well correlated with the inhibitory effects of hypoxia, the levels of PCr are well correlated (Lövgren and Hellstrand, 1985). Any causal relationship between levels of PCr and the inhibitory effects of hypoxia is doubtful, however. Reduction of PCr by feeding rats β-guanidinoproprionic acid did not inhibit spontaneous contractility of the MPV or reduce its maximum response to high potassium, although the content of PCr was reduced to 14% of control (Ekmehag and Hellstrand, 1988). The current thinking of these investigators is that inhibition of intracellular respiration, such as that produced by cyanide, inhibits contractility by several mechanisms including inhibition of phosphorylation of the 20-kilodalton light chains of the myosin molecule (Ekmehag and Hellstrand, 1989).

The structural effects of hypoxia as measured by altered permeability to lanthanum, [^{35}S]sulphate, or [^{14}C] sorbitol have been investigated (Ebeigbe, 1984). Electron microscopy could detect no changes in the distribution of lanthanum, nor were there differences in the radioactive markers, in MPV exposed to hypoxia compared to control veins.

It has been argued that glucose can alter excitability of smooth muscle by means other than its effect on metabolism (Linke and Betz, 1979), but the evidence is difficult to interpret. That view is supported by the observation that there was not a clear relationship between ATP levels and contractility when ATP was depleted by anoxia or fluoroacetate and that 2-deoxy-D-glucose inhibited contraction only in the absence of glucose (Cremer-Lacuara et al., 1980). Subsequent work has verified the dissociation of ATP levels and contractility in the rat MPV and has confirmed the ability of glucose to restore contractility without restoration of ATP levels (Linke et al., 1980). The tissue reduced form of nicotinamide adenine dinucleotide as monitored by surface fluorescence is correlated with spontaneous contraction and relaxation (Linke and Heinle, 1981). After exposure of rat MPV to glucose-free medium, Ruiz et al. (1985) showed that the rate of return of contractility depends on the metabolic substrate added, with pyruvate being more effective than glucose. It may be that glucose has more than metabolic effects, but it is not always clear whether spontaneous contractions or contractures are being monitored in experiments dealing with this topic. Therefore, it is difficult to draw firm conclusions concerning the effects of glucose.

Bovine MPV has been used as a source of subcellular fractions of smooth muscle including mitochondria which can be demonstrated to accumulate calcium in vitro (Vallières et al., 1975). The MPV of horse and of rat also has been used as a source of tissue for ligand-binding studies including putative calcium channels (Dacquet et al., 1989). The rate of synthesis of collagen has been studied in rabbit MPV (Fischer and Swain, 1985). It was much higher in MPV compared to inferior vena cava.

D. Summary

The MPV has been used for biophysical studies including its compliance, stiffness, length-tension relationship, active state, and spectral analysis of its rhythmicity. The effects on electrical and mechanical events of physical factors such as pH, temperature, vibration, stretch, and osmolarity have been examined. Vibration induces relaxation, probably due to an effect on cross-bridges, whereas stretch can initiate electrical and contractile activity. These effects of vibration and stretch may be pertinent to vascular pathophysiology and autoregulation, respectively. The effects of osmolarity on the MPV are inconsistent and confusing, perhaps because time of exposure is a variable that has not been adequately controlled.

Biochemical investigations using the MPV include studies of the sources of its energy and the effects of uncoupling oxidative phosphorylation, hypoxia, and absence of glucose on function and energy supply. The MPV also has been used as a tissue source of subcellular organelles and molecules for uptake and binding studies.

VIII. Receptors

The existence of receptors in a tissue can be demonstrated by the presence of a response to an agonist and the selective reduction of that response by the appropriate antagonist. This technique was used to indicate the presence of α- and β-adrenoceptors, as well as receptors for acetylcholine, histamine, and serotonin, in the rabbit MPV (Sutter, 1965). Receptors for a substance also are presumed when a response to that substance occurs after responses to other agents have been blocked, thus receptors for polypeptides and nonadrenergic-noncholinergic substances (purines) have been demonstrated in the MPV (see section II). The following sections deal with papers in which the nature of receptors has been specifically investigated or a possible selective antagonist for a particular receptor(s) has been studied.

A. α-Adrenoceptors

The distribution of α-adrenoceptors in the rat MPV is not uniform as revealed by visualisation with [^{3}H]noradrenaline, which is distributed mainly between the longitudinal and circular layers. This parallels the distribution of nerves and suggests that the adrenoceptors are localised at sympathetic nerve endings (Ljung et al., 1973).

The MPV of the dog has been used to demonstrate the α-adrenergic blocking properties of droperidol. This drug did not reduce spontaneous contractility of the vein but did inhibit responses to noradrenaline and to nerve stim-

ulation. Release of noradrenaline by nerve stimulation was not affected (Muldoon et al., 1977).

The adrenoceptors in dog MPV that initiate contraction seem of the α_1 and α_2 type because they are blocked by either prazosin or yohimbine (Kou et al., 1984). Use of other agonists and antagonists with selectivity for α_1- and α_2-adrenoceptors such as phenylephrine, UK-14,304, and terazosin led to the same conclusions: both types of adrenoceptors are present postsynaptically in dog MPV (Itoh et al., 1987; Furuta, 1988).

Clonidine (an α_2-adrenoceptor agonist) can reduce the electrically induced release of noradrenaline from rabbit MPV, whereas release is increased equally by the antagonists, rauwolscine or yohimbine, and less so by prazosin. The contractile responses to noradrenaline are equally inhibited by rauwolscine, yohimbine, or prazosin (Docherty and Starke, 1982). These results also indicate that there are presynaptic α_2-adrenoceptors in the rabbit MPV but both α_1- and α_2-adrenoceptors are postsynaptically located. Similar conclusions pertain for the rat MPV (Hicks, 1983a), with the addition that α_1-adrenoceptors are more involved in tonic contractures and α_2-receptors mediate phasic activity. These conclusions were based on the observation that both yohimbine and prazosin were required to competitively antagonise noradrenaline-induced phasic activity. The inhibitory effects of yohimbine on noradrenaline release are attenuated in the presence of ouabain, presumably because inhibition of the sodium pump also promotes release of noradrenaline (Török et al., 1985).

The apparent affinity (pD_2 values) of the α_2-adrenoceptor agonist clonidine for receptors in the rat MPV has been compared with its affinity for receptors in aorta, spleen, bladder, and vas deferens (Ruffolo et al., 1980). The values were 7.8, 6.8, 6.7, 6.5, and 5.9, respectively, which suggest that there are three different adrenoceptors with which clonidine can interact. Similar conclusions, namely, that α-adrenoceptors differ in MPV and aorta, were reached using a variety of agonists and antagonists in the rat (Digges and Summers, 1983). In particular, the pA_2 values for prazosin and phentolamine were an order of magnitude lower in MPV than in aorta.

Not everyone agrees that functional α_2-adrenoceptors are present in rat MPV, however, because the supposedly α_2-selective antagonist rauwolscine does not inhibit prazosin-resistant contractions any better than coryanthine, a supposed α_1-selective antagonist (Downing et al., 1988). The drugs prazosin and tiodazin (α-adrenoceptor antagonists) have been compared on rat MPV and found to be very similar in action; both lack direct vasodilator action and do not interact with presynaptic receptors (Cohen et al., 1980).

The adrenoceptors with which dopamine interacts to induce contraction in the dog MPV seem to be of both α_1 and α_2 type because 10^{-8} M yohimbine or 10^{-9} M prazosin produced similar shifts to the right of the dose-response curve of contraction (Toda et al., 1984). Dopamine has been reported to inhibit spontaneous contractility in the rat MPV in a dose-dependent manner. This inhibition was not blocked by +(D)butaclamol, a dopamine antagonist, but was blocked by ICI 118551, a selective β_2-antagonist. This suggests that β-adrenoceptors and not D_1- or D_2-receptors are involved in the inhibitory effects of dopamine in the rat MPV (Vidal-Beretervide et al., 1988).

Recently, the MPV was used as one of several tissues from rat to study whether differences in potency of enantiomers of adrenaline were due to changes in affinity or efficacy (Rice et al., 1989). After partial adrenoceptor blockade with phenoxybenzamine, Rice et al. used ED_{50} as a measure of affinity. They found that there was a constant ratio between affinity and efficacy for the enantiomers and concluded that the differences in potency between enantiomers are due to differences in affinity.

B. β-Adrenoceptors

The effects of isoprenaline were demonstrated to be dose dependent on the rabbit MPV. At concentrations of 5×10^{-8} M, relaxation and inhibition of spontaneous contractions were produced; whereas at 5×10^{-6} M, contractions occurred. The inhibition was antagonised by the β-adrenoceptor antagonist, pronethalol, whereas the contractions were inhibited by phentolamine. Thus, isoprenaline can activate both α- and β-adrenoceptors in this tissue, but it has selectivity for β-receptors (Sutter, 1965).

The guinea pig MPV was used as one of a battery of tissues to demonstrate that the drug AH 5158 (labetolol) possessed both α- and β-adrenoceptor antagonist properties (Farmer et al., 1972). Similar experiments on the rabbit MPV led to similar conclusions regarding nipradilol, namely, that this drug is an α- and a β-adrenoceptor antagonist (Nanjo and Kitamura, 1984). The guinea pig MPV has been used to demonstrate that the sulphonamide-substituted phenylethylamine derivative, amosulalol, possesses both α- and β-adrenoceptor-blocking properties (Fujioka and Suzuki, 1985). The presence of β-adrenoceptors in rabbit (Mackenzie and Parratt, 1973) and guinea pig MPV (Beckett and Foster, 1972) allowed the drug oxyfedrine to be identified as a partial antagonist by both of these groups.

The β-adrenoceptors on rat MPV have been characterised by the use of selective β-adrenoceptor antagonists to be of the β_2 type. This is in contrast to the rat coronary artery which has β_1-type adrenoceptors (Johansson, 1973b). As mentioned in section II, the rat MPV has been shown to possess presynaptic β-receptors as well (Dahlöf et al., 1978). These are of the β_2 type (Westfall et al., 1979; Dahlöf et al., 1980).

The MPV of the rat has been used to study the interactions of β-agonists and antagonists in comparison with rat atria. The pharmacodynamics were analyzed by Schild plots. It was found that the pA_2 values for the β-

adrenoceptor antagonists atenolol, metoprolol, and pamatol were 10–100 times less in atria than in MPV so that these drugs are selective for cardiac β-adrenoceptors. Johansson (1979) pointed out, however, that the slope of log (dose ratio minus 1) approaches unity only with pamatolol. This suggests that the antagonist/β-adrenoceptor interaction is not competitive for atenolol and metoprolol. Recently, the rat MPV has been suggested to be a good tissue on which to study β-adrenoceptors and their antagonists (Vidal-Beretervide and Castañeda, 1988). Using the selective β_1-antagonist betaxolol, Vidal-Beretervide (1988) confirmed that the β-adrenoceptors in the rat MPV are of the β_2 type.

The interaction between α- and β-adrenergic responses has been examined in rabbit MPV. It was found that propranolol would restore the contractile effect of adrenaline after α-adrenoceptors had been blocked with phenoxybenzamine (Story and Bentley, 1974). The mechanism of this effect of propranolol is not known but the phenomenon also occurs in several other vascular tissues and in vivo (Tabrizchi and Pang, 1988).

C. Cholinoceptors

Binding studies have been done on membrane fractions of homogenised MPV from dog using [^{3}H]quinuclidinylbenzilate as a ligand (Taniguchi et al., 1983). Saturable binding of [^{3}H]quinuclidinylbenzilate was observed and it was displaced competitively by muscarinic agents but not by nicotine, α-bungarotoxin, or hexamethonium. These observations are consistent with the existence of muscarinic receptors in this tissue. Similar experiments were done and similar conclusions reached by others (Milnor and Sastre, 1988). Both circular and longitudinal muscle contract to acetylcholine and to nerve stimulation when adrenoceptor blockade is present so that muscarinic receptors seem to be present in both types of muscle (Yoshioka et al., 1988a).

D. Receptors for Histamine or Serotonin

The receptors for serotonin in the rat MPV are reported to be of the 5-hydroxytryptamine subtype 2 type (Lemberger et al., 1984). The evidence for this is that there was a significant correlation between the affinity of a series of antagonists as determined by their antagonism of contractile responses in the MPV and their ability to bind to 5-hydroxytryptamine subtype 2 sites, but not to 5-hydroxytryptamine subtype 1 sites, in membrane from frontal cortex. The rat MPV thus resembles aorta and caudal artery and differs from the gut regarding the type of serotonin receptors that are present.

Receptors for histamine may be different in the circular muscle of MPV compared to the longitudinal muscle. The longitudinal muscle of rabbit MPV responds more strongly to histamine than does circular muscle (Brown et al., 1982). The receptors in the longitudinal muscle of dog MPV seem of the histamine subtype 1 type and mediate contraction, but in circular muscle histamine subtype 1 and histamine subtype 2 receptors are present because histamine can relax previously contracted circular muscle. This relaxation is inhibited by ranitidine. When the circular muscle is not contracted, histamine produces only contraction which is blocked by pyrilamine (Toshimitsu et al., 1984). It also has been reported that part of the response to histamine in rabbit MPV seems due to interactions with serotonergic receptors (Cook and MacLeod, 1978) because phentolamine blocked the responses to both histamine and noradrenaline and high doses of serotonin produced desensitisation to histamine and to serotonin but not to noradrenaline. Release of noradrenaline also has been invoked as being involved in the responses to histamine in dog MPV because phentolamine or prazosin could block the response but yohimbine could not. Pretreatment with 6-hydroxydopamine also inhibited the response to histamine (Bielkiewicz and Cook, 1984). The use of spirally cut strips which would contain both circular and longitudinal muscle and experiments in different species complicates the interpretation of these results, however.

An inhibitory effect of histamine also has been observed in spirally cut ovine MPV (Mirbahar and Eyre, 1984), but the orientation of muscles in this preparation is not clear. Responses to noradrenaline and to serotonin also were observed in this tissue. It is also possible that histamine exerts part of its effect through release of EDRF (Miyazaki and Toda, 1986).

E. Receptors for Peptides

Receptors for angiotensin in spiral preparations of rat MPV have been inactivated by photoaffinity labeling with [azidobenzoic acid, isoleucine]angiotensin II (Kwok and Moore, 1984). This procedure did not block adrenoceptors and allowed the fraction of "spare" receptors for angiotensin II to be calculated. It was found that approximately 60% of receptors to angiotensin II are spare, whereas there are no spare receptors for angiotensin III. Dissociation constants (K_d) have been estimated, by use of a slowly dissociating angiotensin antagonist [Sar1,Ile8]ANGII, for angiotensin II and III in rat uterus, MPV, and aorta. There was no difference in the K_d values for angiotensin II between any of the tissues or for angiotensin III (Scanlon and Moore, 1988b). The same conclusion was reached when it was observed that the angiotensin antagonist sarmesin had similar pA_2 values in uterus, vein, and MPV (Scanlon and Moore, 1988a). This suggests that the receptors for angiotensin are similar from tissue to tissue. There seems to be cooperation between angiotensin receptors as judged by analysis of dose-response curves using Hanes-Woolf transformations (Moore and Scanlon, 1989).

It appears that receptors for bradykinin can be formed de novo in rabbit MPV. Responses to this substance have been reported to be absent until the tissue has been incubated in vitro and the responses can be prevented selectively by inhibitors of protein synthesis (Regoli et

al., 1978). The bradykinin receptors are distinct from receptors for substance P which also are present in the rabbit MPV (Berube et al., 1978). The receptors for bradykinin have been studied by structural activity techniques and classified to be of the bradykinin subtype 2 type in guinea pig MPV (Gaudreau et al., 1981) but of the bradykinin subtype 1 type in rabbit MPV (Babiuk et al., 1982). Based on studies of binding of bradykinin to whole tissue in vitro it has been suggested that ingestion of lipopolysaccharides leads to increased response of the MPV because of increased number of receptors for bradykinin (Barabe et al., 1982).

It has been suggested that part of the action of bradykinin is due to release of EDRF in dog MPV (Toda et al., 1987). EDRF derived from arteries did not inhibit spontaneous contractility of rat MPV. Vedernikov et al. (1987) and Feletou et al. (1989) concluded that EDRF from arteries acts only as a local regulator of the vasculature. Receptors for EDRF probably do exist in the MPV, at least of dog, because the presence or absence of the endothelium can alter the response to barium or to histamine (Miyazaki and Toda, 1986).

Substance P produces a dose-dependent contraction in rat everted MPV which is inhibited by peptide antagonists of substance P but not by other standard inhibitors of transmitters (Mastrangelo et al., 1983). Mastrangelo et al. concluded that specific receptors for substance P are present in this preparation. Previous investigators (Berube et al., 1978) had reached the same conclusions for the rabbit MPV. Subsequent investigations (Regoli et al., 1984) indicated that the responses to substance P are independent of the endothelium in the MPV and not due to release of substances such as prostaglandin. Rabbit MPV has been used as one of the test tissues in an attempt to develop a substance P antagonist (Caranikas et al., 1982). It is now suggested that there are several types of receptors for the family of peptides termed the neurokinins and which includes substance P. Rat MPV is reported to contain receptors of the neurokinin B type (Dion et al., 1987; Mastrangelo et al., 1987). Selective antagonists have been attempted to be made and have been tested on the rat MPV (Drapeau et al., 1987; Rovero et al., 1987; Hashimoto et al., 1987). Hashimoto et al. reported that [Gly6]-neurokinin B type [3–10] is a competitive antagonist of neurokinin B type in this tissue.

The rat MPV has been used to test neurotensin and several of its fragments and analogues for agonist/antagonist activity (Rioux et al., 1980b). The pD_2 values of two of the analogues were similar in MPV and rat coronary vessels, which suggests that the receptors for neurotensin are similar in these two tissues.

VIP can be demonstrated to have a concentration-dependent inhibitory effect on spontaneous contractility of rat MPV (Brätveit and Helle, 1984) that is not blocked by atropine or β-adrenoceptor antagonists and is not dependent on opioids or neurotensin. VIP seems to be less effective in relaxing the inner circular layer of muscle compared to the outer longitudinal muscle of the rat MPV, whereas isoprenaline was equally effective on either muscle (Rydningen et al., 1987).

Atriopeptins II and III (atrionatriuretic peptides) also can relax the rat MPV. Atriopeptin II is less potent on circular muscle than on longitudinal muscle but atriopeptin II and III are equipotent on longitudinal muscle (Brätveit et al., 1987).

It is suggested that presynaptic opioid receptors of the κ- and δ-type are present in rabbit MPV and that their activation can inhibit neurogenic release of noradrenaline (Szabo et al., 1987). The evidence for this is that κ- and δ-selective opioid agonists, but not μ-selectve ones, inhibited the contractile responses to electrical stimulation of strips of rabbit MPV. Naloxone shifted the curve of dose inhibition to the right.

F. Other Receptors

Kennedy and Burnstock (1984) attempted to characterise the purinergic receptors involved in prejunctional events in rat MPV using a number of adenosine derivatives. These investigators argued that the pattern of inhibition produced by these analogues on contraction induced by nerve stimulation is of a particular type which they label A_2. In this regard the rat MPV is special in that other adrenergic or cholinergic junctions display characteristics of the A_1 type of purine receptor.

ATP analogues also have been examined in rat MPV. ATP contracts this MPV and increases electrical spiking as well as depolarises the membrane. Desensitisation to ATP can be produced, leaving responses to noradrenaline intact. On the basis of the order of potency of the ATP analogues, the receptors have been labeled purinergic, of the P_{2X} subtype (Reilly and Burnstock, 1987). The function and characterisation of purinergic receptors are difficult, however, because there does not exist a selective, competitive purinergic antagonist (Reilly et al., 1987).

A beginning toward the classification of prostaglandin receptors in the rat MPV helical strip has been made (Eglen and Whiting, 1988). A series of agonists (prostaglandin D_2, E_1, E_2, and others) and two putative selective antagonists (AH 6809 and SQ 29, 548) were used, and the receptors for prostaglandin in MPV and aorta were found to be similar and classified as TP receptors.

G. Summary

The adrenergic receptors in the MPV seem to be located primarily near sympathetic nerve terminals. The α-adrenoceptors are primarily of the α_2 type presynaptically where they can modulate noradrenaline release. Postsynaptically they seem of both α_1 and α_2 type. Dopamine interacts with α- or β-adrenoceptors. β-Adrenoceptors functionally can be demonstrated both pre- and postsynaptically. They are of the β_2 type. Muscarinic cholinoceptors are present in the MPV where they me-

diate contraction independently of endothelium. Serotonin initiates contraction via 5-hydroxytryptamine subtype 2 receptors. Histamine constricts longitudinal muscle by interaction with receptors of the histamine subtype 1 type but both subtype 1 and 2 receptors seem to be present in circular muscle where subtype 2 receptors may be involved in relaxation. Receptors for angiotensin, bradykinin, substance P, neurotensin, VIP, atriopeptides, and opioids are present in the MPV. The receptors for opioids are presynaptic. Attempts have been made to identify and classify the receptors for purines and prostaglandins in the MPV.

IX. Relaxation and Inhibition

A. Adrenergic Effects

The MPV is one of the few isolated blood vessels that possesses intrinsic tone so that relaxants can be studied in the absence of another agent to produce contraction. One of the first questions asked was whether membrane spike frequency paralleled loss of tension during relaxation of the rabbit MPV. It was observed that this was the case for relaxation produced by theophylline or isoprenaline but not relaxation produced by removal of external calcium (Cuthbert and Sutter, 1965). In the latter situation, contractile activity decreased before action potential frequency decreased.

The ability of isoprenaline to relax the MPV and decrease spike frequency was similar in the rat (Johansson et al., 1967) as in the rabbit. Other β_2-agonists such as salbutamol and AQ 110 also relaxed the rabbit MPV (Fogelman and Grundy, 1970).

Mephentermine has been reported to relax the rabbit MPV but only if the adrenergic antagonist phenoxybenzamine was present (Caldwell and Goldberg, 1970). The relaxation was not blocked by the β-antagonist MJ-1999, however, which suggests that β-adrenoceptors are not involved.

The effect of cocaine on relaxation rate of rabbit MPV after transmural stimulation and after application of noradrenaline has been examined. Cocaine potentiated and prolonged responses to endogenous and exogenous noradrenaline. Relaxation was not affected by hydrocortisone or 4-aminopyridine. The chief determinant of termination of responses to noradrenaline, therefore, seems to be neuronal uptake (Paton, 1980).

B. Cyclic AMP and Other Intracellular Messengers

As mentioned previously, theophylline which was known to be a phosphodiesterase inhibitor was shown to inhibit spontaneous activity in rabbit MPV (Cuthbert and Sutter, 1965). This was confirmed for rat MPV and it was further shown that cyclic AMP and dibutyryl cyclic AMP also inhibited spontaneous contractility in this vein (Berti et al., 1970). The ability of a series of cyclic AMP analogues to relax the guinea pig MPV also has been reported (Rubin et al., 1971).

The relationship between the intracellular concentration of cyclic AMP and relaxation produced by a variety of agents has been investigated. It was observed that there is a direct relationship between cyclic AMP levels and degree of relaxation only when the relaxant is isoprenaline. This is true for rat (Ljung et al., 1975a) or rabbit MPV (Collins and Sutter, 1975). Agents such as papaverine cause cyclic AMP to increase rapidly and markedly but relaxation develops only slowly with this agent. The correlation between the degree of relaxation and the amount of cyclic AMP which is produced by treatment with phosphodiesterase inhibitors holds only for an individual agent and does not hold between agents.

The relation between relaxation produced by isoprenaline and cyclic AMP-dependent protein kinase has been examined in dog MPV. Isoprenaline increased the kinase activity but the increase was not proportional to relaxation (Kikkawa et al., 1986). Increased lactate production is not a requisite for relaxation induced by either isoprenaline or papaverine in the rat MPV (Lövgren and Hellstrand, 1987).

The relaxation produced by isoprenaline is associated with a decrease in internal calcium as measured by aequorin luminescence. In contrast, relaxation produced by papaverine is not accompanied by decreased luminescence (Morgan and Morgan, 1984b).

Sodium must be present in the bath fluid in order for relaxation to occur with isoprenaline. It was suggested that sodium-calcium exchange is involved in relaxation produced by isoprenaline but not by papaverine (Collins and Sutter, 1975). Isoprenaline is less able to relax the rat MPV when strontium is substituted for calcium (Arner et al., 1983) and this is consistent with the suggestion that sodium-calcium exchange occurs assuming that strontium is less well handled by such an exchange system.

C. Ions and Ion Permeability

Diazoxide, an antihypertensive drug that is chemically related to the thiazide diuretics but causes sodium retention, inhibits electrical activity and contractility in the rabbit MPV (Rhodes and Sutter, 1971a). These effects were attributed to interference with calcium movements but it subsequently has been shown that diazoxide is a potassium channel activator (Quast and Cook, 1989). The natriuretic, antihypertensive drug furosemide also was found to decrease the amplitude of spontaneous contractions and to decrease the contractile responses of rat MPV to noradrenaline (Blair-West, et al., 1972; Biamino et al., 1975b). There is a report that furosemide can induce a dose-dependent contracture of rat MPV (Tayo and Fasanmi, 1984), but the contractions were said to be inhibited reversibly by phenoxybenzamine. The latter usually inhibits by irreversible adrenoceptor blockade, so these experiments are difficult to interpret. Ethacrynic acid inhibited spontaneous contractility and chlorothiazide had no effect on spontaneous contractions

but did inhibit responses to noradrenaline (Tayo and Fasanmi, 1984). Piretamide, an analogue of furosemide, decreases spontaneous contractions of rat MPV in a dose-related manner (Lacuara et al., 1985). Chlorthalidone, another natriuretic, also decreased responses of the dog MPV to noradrenaline after chronic treatment (Zsotèr et al., 1972). Zsotèr et al. (1974) also studied the effects of diazoxide on calcium movements in rabbit MPV and found that the calcium content of the tissue was not altered but that $^{45}Ca^{2+}$ efflux was increased by this drug.

The calcium antagonists vary in their potency, rate of onset, and ability to inhibit spontaneous contractions as compared to those produced by agonists. Presumably this is because the handling of calcium by the tissue can vary with the nature of the contractile stimulus. Verapamil has been shown to abolish spontaneous contractions at 10^{-6} M and to abolish electrical spiking at 10^{-5} M in guinea pig MPV (Golenhofen and Lammel, 1972). Methoxyverapamil (gallopamil, D600) also inhibits spontaneous contractions of rat MPV, but only the (−)-isomer is effective (Jim et al., 1981). It is of interest that the drug flunarizine, which can be demonstrated to inhibit some actions of calcium, does not inhibit spontaneous contractions of rat MPV (Van Nueten et al., 1978a; 1978b; Nakayama and Kasuya, 1980). Diltiazem is less effective in inhibition of spontaneous contractions of rat MPV than it is in antagonising contractions produced by agonists (Hicks, 1983b). The rank order of potency of several calcium antagonists in inhibiting spontaneous contractions in rat MPV is nifedipine, methoxyverapamil (D600, gallopamil), and diltiazem (Granger et al., 1985). The ability of diltiazem and some of its metabolites to inhibit spontaneous activity in rat MPV has been correlated positively with binding of these agents to putative calcium-binding sites in rat cerebral cortex (Schoemaker et al., 1987). Another calcium antagonist felodipine also inhibits spontaneous contractions of cat MPV and at nanomolar concentrations (Reinish et al., 1986). Tienilic acid is another compound that can suppress the increasing phase (calcium current) of action potentials as well as the accompanying contractions in rat MPV (Mironneau et al., 1984). Presumably this is due to interference with spontaneous activation of calcium channels.

The sensitivity of the rabbit MPV to the calcium antagonist nicardipine has been compared with the sensitivity of the cerebral basilar artery to this drug. It has been suggested that the MPV is less sensitive (Takayanagi et al., 1986), but because maximum responses were not reported, it is difficult to compare the potency of inhibitors. Differences can be shown between calcium antagonists and supposed calmodulin antagonists on spontaneous contractions: the calcium antagonists decrease frequency, whereas calmodulin antagonists such as W7 increase frequency of spontaneous contractions (Campbell et al., 1986). By this and other criteria, bepridil seems to have actions additional to those of calcium antagonism at the surface of the membrane. The antihypertensive drug indapamide decreases action potential amplitude and its accompanying spontaneous contraction (Mironneau and Gargouil, 1979; Mironneau et al., 1986). The several calcium antagonists differ in their onset and potency of inhibition of contractions. The dihydropyridines such as nifedipine are more rapid in onset than are the verapamil type (Dacquet et al., 1987b; Sutter et al.,1988; Mariott, 1988).

Spironolactone also has been found to inhibit spontaneous contractions of rat MPV and to decrease calcium currents in cells dissociated from the vein (Dacquet et al., 1987a). Spironolactone thus seems to be capable of calcium antagonist activity.

Verapamil and the antihypertensive drug BRL 34915 (cromakalim) have been compared on the rat MPV. Both inhibit spontaneous contractions but verapamil depolarises, whereas BRL 34915 hyperpolarises, the membrane. The latter drug increases the rate constant of ^{86}Rb efflux and verapamil does not alter this parameter (Hamilton et al., 1986). Cromakalim reduces the frequency of spontaneous contractions and the IC_{50} for this effect is 0.13 μM (Hof et al., 1988). Nicorandil and cromakalim have similar effects on the rat MPV and Weir and Weston (1986) concluded that both of these agents activate membrane potassium channels with consequent hyperpolarisation. Similar conclusions were reached for pinacidil using the guinea pig MPV (Bray et al., 1987; Cook et al., 1988) and rat MPV (Southerton et al., 1988). Analogues of pinacidil, P1060 and P1368 also have been studied on rat MPV (Weston et al., 1988).

The increased efflux of rubidium induced by cromakalim was inhibited by tetraethylammonium but not by calcium antagonists or by permeable derivatives of cyclic AMP or guanosine monophosphate in guinea pig MPV (Quast, 1987). Quast concluded that cromakalim directly activates potassium channels. He also pointed out that there was a 5-fold discrepancy between the concentration of cromakalim that inhibits contractility and that necessary to increase rubidium efflux. When ^{42}K is used instead of ^{86}Rb the difference between the concentration of cromakalim that will inhibit spontaneous contractility and the concentration required to increase potassium efflux is less but still exists (Quast and Baumlin, 1988). A difference of 10-fold also has been observed between the concentration of cromakalim necessary to inhibit spontaneous contractions and those induced by noradrenaline, the spontaneous contractility being more sensitive (Shetty and Weiss, 1987).

The venom of the Israeli scorpion, *Leiurus quinquestriatus*, inhibits the increase in ^{86}Rb efflux induced by cromakalim. The venom itself increases spontaneous contractility, but appropriate controls were done and it was shown that the inhibition of the increased efflux was

independent of the contractile effects of the venom (Quast and Cook, 1988). The oral hypoglycemic agent glibenclanide (glyburide) also inhibits the ability of cromakalim to increase ^{86}Rb efflux in rat MPV and prevents cromakalim from inhibiting spontaneous contractions (Buckingham et al., 1989). Glibenclamide also inhibits the ability of diazoxide to inhibit spontaneous contractions and interferes with the increase in ^{86}Rb efflux which diazoxide causes (Quast and Cook, 1989). It seems that cromakalim and diazoxide act at least in part through similar mechanisms, namely, activation of a potassium channel which leads to hyperpolarisation of the membrane. Glibenclamide has the opposite effect.

Activation of the sodium pump with resultant electrogenesis seems able to relax the MPV. This was demonstrated in longitudinal strips of dog MPV when restoration of potassium was shown to relax the vein that has been contracted by addition of noradrenaline to potassium-free solutions. This relaxation was blocked by the ouabain-like compound 14β-hydroxyprogesterone (Bose et al., 1988).

Removal of external calcium or addition of manganese also inhibits spontaneous contractions and relaxes the rabbit MPV (Collins et al., 1972a; 1972b). Similar findings have been described for guinea pig MPV with the additional observation that lanthanum, 0.16 mM, eliminates spontaneous activity (Uchida, 1975). The effects of manganese differ from those of other cations (see section V, D) in that when manganese is present in the extracellular period for more than 0.5 h, its inhibitory effects start to disappear. Presumably, this is because manganese can slowly permeate inside the cell where it increases the size of contraction. Other ions such as Mg^{2+}, Cd^{2+}, La^{3+}, Ni^{2+}, or Sn^{2+} persist as inhibitors of contraction as long as they are present. It seems that, when it is outside the cell, manganese slows the rate of contraction and speeds relaxation but has additional effects after it has entered the cell (Sutter et al., 1988).

Copper has been shown to have a concentration-dependent effect on spontaneous contractility in the rat MPV: an initial increased rate and decreased amplitude of contractions and their abolition as the concentration is increased (Larsson et al., 1976).

D. Miscellaneous Agents

The antimalarial agents chloroquine and mepacrine have been found to inhibit spontaneous contractions in rat MPV (Minker et al., 1980).

Prostaglandin E_1 relaxes the MPV from rabbit, whereas prostaglandin $F_{1\alpha}$ and $F_{2\alpha}$ produce contraction (Kadar and Sunahara, 1969). The relaxation is accompanied by hyperpolarisation of the membrane (Kitamura et al., 1976). Prostacyclin I_2 also inhibits spontaneous contractions of the MPV from dog (Herman et al., 1978) but has been reported to only stimulate spontaneous contractility in rat MPV (Levy, 1978). The prostaglandin synthetase inhibitor sodium meclofenamate also has been reported to inhibit spontaneous contractility of rat MPV (Enero, 1979).

Oxytocin has been reported to inhibit spontaneous contractility of guinea pig MPV (Milenov et al., 1979). The effect of pregnancy and hormones of pregnancy have been examined in rat MPV (McCalden, 1975). Progesterone was found to inhibit spontaneous contractions, whereas oestradiol-17β had a biphasic effect: stimulation at lower and inhibition at higher concentrations. The potency of progesterone increased with the duration of gestation.

The gastrointestinal hormones secretin and cholecystokinin reduce the amplitude and increase the frequency of spontaneous contractions of the rat MPV (Fara, 1975). The two effects were additive, not blocked by propranolol, and were increased by theophylline so that Fara concluded that both secretin and cholecystokinin were acting through increase in cyclic AMP.

Pentobarbital at a concentration of 10^{-5} M inhibits spontaneous contractions in rat MPV (Altura and Altura, 1975). At concentrations of 10^{-4}-10^{-3} M pentobarbital is reported to reduce exchangeable calcium in this tissue (Altura et al., 1980c). There thus is a discrepancy between the concentrations that inhibit spontaneous contractions and those that alter calcium kinetics. Thiopental, althesin, and ketamine also decrease the amplitude of spontaneous contractions in rat MPV (Hall and Pleuvry, 1979; Altura et al., 1980a). Urethane similarly inhibits spontaneous contractions of rat MPV (Altura and Weinberg, 1979). Halothane or thiopental also have been shown to inhibit spontaneous contractility of rabbit MPV (Clark and MacCannell, 1975) so that the inhibitory effect seems to be widespread among agents used to produce general anaesthesia.

Ethanol also is inhibitory to spontaneous contractions at a concentration of 17 mM and inhibits stimulated contractions to noradrenaline and potassium at higher (100–170 mM) concentrations (Edgarian and Altura, 1976). Both amplitude and frequency of contractions are reduced (Yang et al., 1987). Ethanol also has been reported to reduce the concentration of calcium in rat MPV (Turlapaty et al., 1979a). The relation between calcium content and relaxation is unclear.

Sodium nitroprusside inhibits spontaneous contractility of dog (Verhaeghe and Shepherd, 1976) and rat (Sunano, 1984a; 1984b) MPV but is reported not to inhibit noradrenaline-induced contractions in rat MPV (Jetley and Weston, 1980). In rabbit MPV sodium nitroprusside increases efflux but not uptake of $^{45}Ca^{2+}$ in a dose-related manner (Zsotèr et al., 1977) but how this is related to relaxation is unknown. Glyceryl trinitrate, pentaerythritol tetranitrate, and sodium nitrate all have been demonstrated to inhibit spontaneous contractility as well as noradrenaline-induced contractions in rat MPV (Mackenzie and Parratt, 1977). The action of glyceryl trinitrate is accompanied by a biphasic effect on membrane poten-

tial of rat and guinea pig MPV: a hyperpolarisation followed by a depolarisation (Karashima, 1980). In guinea pig MPV the coronary vasodilator 2-nicotinamidoethyl nitrate similarly hyperpolarises the membrane and inhibits spontaneous contractions (Karashima et al., 1982). Isosorbide dinitrate has been reported not to have an effect on membrane potential of spiral strips of rabbit MPV and to have no effect on skinned fibres even though inhibition of responses occurred in intact tissue (Ishikawa et al., 1983). The use of spiral strips complicates the interpretation of these observations.

ATP can relax the MPV of rat and rabbit (Su, 1975 ; 1978) but contracts the MPV of guinea pig (Burnstock et al., 1979). It also has been reported that ATP and AMP increase spike frequency in rat MPV (Karashima and Takata, 1979). The relation between the electrical and mechanical events produced by purines is unclear (see also sections II and VII).

VIP mimics the relaxation produced by transmural stimulation of the rat MPV in that relaxation produced by VIP is of slow onset and offset. This is distinct from relaxation produced by adenosine which has a rapid onset and recovery (Ishii and Shimo, 1983) (see also sections II, D, and VII, E). It is of interest that apamin, a bee venom that interferes with vasodilation produced by stimulation of nerves in the cat intestine in situ, does not antagonise the effects of VIP on rat MPV in vitro (Jodal et al., 1983). The inhibitory effects of VIP, isoprenaline, and atriopeptins II and III have been compared on rat MPV (Brätveit et al., 1987). The maximum effect of VIP and of isoprenaline was greater than that of the atriopeptins.

E. Physical Factors

Cooling has been shown to relax the MPV and to inhibit spontaneous activity (Vanhoutte and Lorenz, 1970). Vibration also induces relaxation of rat MPV at any stage of the contraction cycle (Ljung and Sivertsson, 1972; 1975; Ljung and Hallgren, 1975).

Age of the animal from which the tissue is taken does not seem to affect the ability of rat or rabbit MPV to relax to isoprenaline or nitroglycerine, although relaxation of arteries from these same animals can be decreased by age (Fleisch and Hooker, 1976).

F. Summary

β_2-Adrenergic agonists such as isoprenaline inhibit spontaneous activity of the MPV. In so doing they decrease electrical spiking and increase cyclic AMP in the tissue. Theophylline and papaverine also increase cyclic AMP and relax the MPV, but the quantitative and temporal correlations suggest that the increase in cyclic AMP is not causally related to the relaxation. Isoprenaline decreases calcium luminescence but papaverine does not. Extracellular sodium is required for isoprenaline-induced relaxation. Natriuretics such as furosemide inhibit spontaneous contractility as do the various calcium antagonists such as verapamil or nifedepine. The potency and rapidity of onset vary among the several calcium antagonists. Manganese and several other cations (Mg^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+}, Sn^{2+}, La^{3+}) inhibit spontaneous activity and responses to agonists but manganese is unusual among these ions in that it loses its ability to inhibit the magnitude of contractile response in spite of its continued presence in external fluid. Cromakalim, pinacidil, and diazoxide inhibit spontaneous contractions and increase efflux of potassium from the MPV, most likely by activation of potassium channels. Glibenclamide, an oral hypoglycemic agent, interferes with the relaxation and efflux of potassium induced by cromakalim, pinacidil, and diazoxide. A number of unrelated substances can be shown to inhibit spontaneous contractions: prostaglandin E, prostacyclin, oxytocin, general anaesthetics such as barbiturates, urethane, and ethanol, the nitrates, adenosine, and several peptides such as VIP, and the atriopeptins. Cooling and vibration inhibit contractility too.

X. Drug Effects (including Peptides)

A number of drugs that are not readily classified have been studied on the MPV. These drugs will be discussed in the following section and, in particular, the drug felodipine will be mentioned first because it was discovered by use of the rat MPV as a model of the vasculature.

A. Felodipine

The rat MPV was used as a bioassay in comparison with rat atria to search for a calcium antagonist that was selectively active on the MPV. The thinking behind this was that the MPV functionally resembles the resistance vessels, and if a compound could be found that would have selectivity for such blood vessels, this would be a useful drug (Ljung, 1985). Many compounds were tested until one was found that had marked selectivity for inhibition of responses in the MPV compared to rat atria. This drug was felodipine which has proven to be an effective antihypertensive agent. The view that the MPV is a useful analogue of resistance vessels seems justified in this case.

B. Local Anaesthetics

The local anaesthetics lidocaine or procaine produce a contraction of cat and rat MPV that is not blocked by adrenoceptor antagonists but is prevented by treatment with ouabain (Sanders, 1969). As mentioned in section III, B, ouabain had been shown to depolarise the membrane and to decrease the intracellular potassium concentration of the MPV (Matthews and Sutter, 1967); therefore, it was concluded that local anaesthetics required an electrically excitable membrane to allow their constrictor action to occur. [The excitatory effect of local anaesthetics now likely would be attributed to their ability to inhibit the activation of potassium channels (Hara et al., 1980).] The effects of mepivicaine and

bupivicaine are similar: contraction of the rat MPV followed by relaxation (Åberg and Wahlström, 1972). When the isomers of mepivicaine were used it was found that the L(+)-isomer contracted and the D(+)-isomer relaxed the vein. The relaxation could be overcome by addition of calcium, strontium, or barium (Åberg and Andersson, 1972). Pentacaine and heptacaine are reported to have similar effects, excitation followed by relaxation (Török et al., 1986).

C. Prostaglandins

Ouabain also inhibited the contractile effects of prostaglandin $F_{1\alpha}$ but not that of prostaglandin $F_{2\alpha}$ on dog MPV (Kadar and Sunahara, 1969). This suggests that the prostaglandins can constrict blood vessels by more than one mechanism. Prostaglandin $F_{2\alpha}$ also has been reported to potentiate the responses of dog MPV to serotonin, angiotensin, and noradrenaline and the potentiation to the first two agents was abolished by pretreatment of the animal with reserpine; the facilitation of the response to noradrenaline was not affected (Greenberg et al., 1973a). Prostaglandin B_2 shifts to the left responses of the dog MPV to noradrenaline, potassium, or barium (Greenberg et al., 1975). Arachidonic peroxide was found to increase the rate of spontaneous contractions on murine MPV and this was inhibited 50% by sodium salicylate, 100 μg/ml, and 70% by phenylbutazone, 10 μg/ml, but indomethacin had little effect (Helfer and Jaques, 1974) The anti-inflammatory drug prodolic acid also potentiates the response of rabbit MPV to electrical stimulation but not to noradrenaline (Greenberg, 1975b), presumably by inhibition of the synthesis of prostaglandins which, in turn, can inhibit noradrenaline release (see section II). It has been found that the saponin aescin from the horse chestnut induced contraction of rat and rabbit MPV which was inhibited by indomethacin. The contractile effect was attributed to the ability of aescin to induce synthesis of prostaglandin $F_{2\alpha}$ in the vein as it does in lung (Berti et al., 1977).

D. Opioids and Antidepressants

The effect of morphine and several cogeners were examined in rabbit MPV and they were found to increase spontaneous contractions but to reduce baseline tension (Grundy, 1971).

Methionine-enkephalin increases spontaneous contractions of rat MPV and increases frequency of spiking without depolarisation. These effects are not blocked by nalorphine, however (Yamamoto et al., 1984). One wonders whether this is simply due to a local anaesthetic effect of the enkephalin whereby it interferes with activation of potassium channels. It also is possible that release of catecholamines is involved.

A novel bicyclic antidepressant LU3–010 has been studied as to its effect on noradrenergic transmission in rat MPV. At concentrations of 10^{-7} g/ml it potentiated the effects of field stimulation, but at higher concentrations it decreased the responses (Häggendal et al., 1972b).

E. Drugs Interacting with the Adrenergic System

Ergometrine has been reported to interact directly with α-adrenoceptors in rabbit MPV to contract this tissue (Wassef et al., 1974). Ajmaline (rauwolfine) increases the amplitude of spontaneous contractions in rat MPV by an unknown mechanism (Biamino et al., 1975a).

The effects of tetrabenazine on catecholamine content have been explored in rat MPV. This drug markedly diminished histofluorescence after intraperitoneal administration and decreased the response to transmural stimulation. The histochemical appearance and response to electrical stimulation were restored by incubation with noradrenaline. In contrast, the effects of reserpine were not reversed by incubation with noradrenaline (Tomlinson, 1977).

Tomlinson reported that the neuromuscular blocking agent pancuronium shifts noradrenaline dose-contraction response curves to the left in rat MPV. The response to St 91, an α-adrenergic agonist that is not taken up by the uptake$_1$ system for noradrenaline, was not altered by pancuronium. Tomlinson (1979) concluded that pancuronium blocks uptake$_1$ in rat MPV.

Cocaine potentiates the responses to noradrenaline in the MPV of guinea pig, rat, rabbit, and dog (Kaiman and Shibata, 1978a, O'Conner and Slater, 1981a; 1981b) but the mechanism still is uncertain.

Recently, the rat MPV has been used to attempt to characterise a new possible α-adrenoceptor agonist, S.3341 (Bourreau et al., 1988). This drug was found to inhibit the amplitude of spontaneous contractions at concentrations less than 10^{-6} M and to increase them at concentrations above this. The latter effect was blocked by prazosin. S.3341 could antagonise the stimulant effects of clonidine or phenylephrine. Bourreau et al. suggest that S.3341 is an α_1-adrenoceptor partial agonist.

F. Drugs Affecting Calcium Handling

The effects of the tremor-producing iboga alkaloid tabernanthine have been examined on the rat MPV. The drug was found to inhibit the response to noradrenaline, but to increase spontaneous contractility. Miller and Godfraind (1983) suggest that it is a partial calcium agonist. This is a fascinating concept but would be difficult to differentiate from a drug that acted differently on the several calcium channels or sources involved in spontaneous versus induced contractions.

The effect of the excitatory dihydropyridine BAY K 8644 has been studied in rat MPV. This drug increased spontaneous contractility at low (10^{-8}-10^{-6} M) and decreased contractility at high (10^{-5} M) concentrations. The stimulation of spontaneous contractions was blocked by nifedipine or the absence of calcium. It was concluded that BAY K 8644 increased calcium entry at low and reduced it at high concentrations (Mikkelsen,

1985). It would have been interesting to have compared the optical isomers of BAY K 8644 in these experiments. BAY K 8644 was compared with another dihydropyridine, CGP 28392, on spontaneous contractility and the latter was found to be less potent (Mikkelsen et al., 1985). The responses of the tissue to BAY K 8644 were more reduced than were the responses to CGP 2892 by exposure of the MPV and drug to ultraviolet radiation even though CGP 2892 itself was more sensitive to radiation. Mikkelsen et al. suggested that ultraviolet light has a direct effect on the interaction of tissue and BAY K 8644.

The effects of chronic treatment of rats with gallopamil (D600) have been examined on the response of the MPV (Pang and Sutter, 1985). Such treatment increased the spontaneous contractility in normal calcium solutions and increased the responses of the MPV to noradrenaline and to potassium when external calcium was reduced. Chronic treatment with hydralazine did not produce these effects. We concluded that chronic treatment with gallopamil decreases the requirements for calcium in the MPV tested in vitro.

The antithrombotic drug suloctidil has antiplatelet action in vivo and has been shown to increase release of prostacyclin from dog MPV in vitro. Suloctidil has been termed a calcium antagonist, but neither verapamil nor flunarazine have similar effects on prostacyclin (Boeynaems et al. , 1987).

The interrelationship between concentration of external calcium and the antagonism by felodipine, diltiazem, or verapamil on contractile responses to noradrenaline has been studied in rat MPV. All of the antagonists reduced the maximum responses to noradrenaline and did not shift the dose-response curve to the right (Ljung and Kjellstadt, 1987). Others report that verapamil but not diltiazem can shift noradrenaline dose-response curves in rabbit aorta and could interfere with the action of phenoxybenzamine in the MPV. It is likely that verapamil has some adrenoceptor-blocking properties in addition to its calcium antagonist ones (Koike et al., 1988).

G. Platelet-Activating Factor

The effects of PAF-acether and a putative antagonist BN 52021 have been studied in rat MPV (Baranes et al., 1986). PAF-acether increased the tone of the MPV and this effect was prevented by BN 52021 without inhibition of spontaneous contractions. The increase in tone produced by PAF-acether is not blocked by atrial natriuretic factor or by sodium nitroprusside but is inhibited by dibutyryl-cyclic AMP (Hellegouarch et al., 1988a). Salbutamol, theophylline, forskolin, and the drug BN 52063 (a mixture of compounds) also can inhibit the contractile effects of PAF-acether on rat MPV. Spontaneous contractions are inhibited by the first two agents but not by forskolin or BN 52063 (Hellegouarch et al., 1988b).

H. Peptides and Proteins

Angiotensin II was the first peptide to be tried on the MPV. It was found to stimulate contraction of rabbit (Sutter, 1965) and rat MPV (Bohr and Uchida, 1967). Action potential frequency parallels the increase in tension in rabbit MPV (Cuthbert and Sutter, 1965) and in rat MPV (Hamon and Worcel, (1982). Although it was known that angiotensin II could increase noradrenaline released during transmural stimulation (Hughes and Roth, 1971), it was concluded that angiotensin II acts directly to contract the MPV of rat, rabbit, guinea pig, and sheep (Blair-West et al., 1971). Among the species, angiotensin II is most potent on the rat compared to rabbit and guinea pig MPV (Carruba et al., 1973). Indeed, angiotensin has been reported to have inhibitory as well as excitatory effects on guinea pig MPV but was only excitatory on rat and rabbit MPV (Weston and Golenhofen, 1976). The inhibitory effects were accompanied by hyperpolarisation and were not blocked by phentolamine plus propranolol.

Vasopressin had been found to be ineffective in causing contraction of rabbit MPV (Sutter, 1965). It subsequently was reported that vasopressin was inhibitory to rabbit and guinea pig MPV but both excitatory and inhibitory to rat MPV (Weston and Golenhofen, 1976). A recent report confirms that vasopressin has no effect on guinea pig MPV in concentrations up to 0.1 units/ml (Karashima, 1981).

Bradykinin early was shown to contract strips of rabbit (Sutter, 1965) and dog (DePasquale and Burch, 1968) MPV (see section VII). Eledoisin also has been reported to contract rat MPV (Mastrangelo and Mathison, 1983).

A host of other peptides were examined for their effects on contractility of the rat MPV (Hellstrand and Järhult, 1980). Bombesin, caerulein, glucagon, insulin, pentagastrin, secretin, somatostatin, substance P, and VIP were tested. Only substance P and VIP had an effect. Substance P increased mean (integrated) tension, whereas VIP had inhibitory effects. The ED_{50} values were 1 M and 1 nM, respectively. On the other hand, caerulein and cholecystokinin as well as substance P have been reported to contract the guinea pig MPV (Zetler and Overbeck, 1987). The species of animal may be important because cholecystokinin previously had been reported to have inhibitory effects on rat MPV (Fara, 1975).

A marine polypeptide *Goniopora* toxin, which produces positive cardiac inotropy, has been tested on guinea pig MPV (Muramatsu et al., 1980). The toxin did not affect resting tone, spontaneous contractility, or responses to noradrenaline. It did alter the response to nerve stimulation and increased the release of ^3H from electrically stimulated veins previously loaded with [^3H]noradrenaline. The increased release of ^3H was abolished by tetrodotoxin or bretylium. Muramatsu et al. concluded that *Goniopora* toxin acts on nerve terminals to increase the

release of noradrenaline induced by electrical stimulation.

Neurotensin, a tridecapeptide, induces contractions of the rat MPV with a pD_2 of approximately 7.5. Tachyphylaxis to its effect readily occurs, however (Helle et al., 1980). It has been suggested that prostaglandins are involved in the response to neurotensin in the MPV (Rioux, et al., 1980a).

Neuropeptide Y has been reported to decrease the release of noradrenaline in response to transmural stimulation of rat MPV but to increase the accompanying contraction. A dual action of this peptide, therefore, is proposed (Dahlöf et al., 1985). Neuropeptide Y itself increases spontaneous motility. The effect on catecholamine release was not altered by phentolamine (Pernow et al., 1986).

Endothelin has been tested on the rat MPV and found to produce contraction that is unaffected by tetrodotoxin or by removal of sodium chloride. The contractions are prevented by removal of calcium from or by addition of nitrendipine to the bathing fluid (Borges et al., 1989). Borges et al. suggested that these findings are consistent with the idea that endothelin acts at a site closely coupled to the calcium channel. It should be noted, however, that noradrenaline also shows the same characteristic lack of dependence on sodium and dependence on external calcium that they observed for endothelin.

We recently studied the effects of several proteins from human plasma on spontaneous contractility of rat MPV (Pillai and Sutter, 1990). We found that albumin increases amplitude and rate of these contractions in a dose-related fashion by a adrenomimetic effect, because it was inhibited by phentolamine but not by in vitro treatment with either 6-hydroxydopamine or by ouabain. In contrast, α-globulin or α- and β-globulin together produced a dose-dependent inhibition of spontaneous contractility. γ-Globulin or the major immunoglobulin, IgG, stimulated spontaneous contractility, again in a dose-dependent manner. This effect was not inhibited by phentolamine, atropine, ketanserin, diphenhydramine, saralasin, or vasopressin antagonists but was inhibited by verapamil or ouabain. The plasma proteins thus seem to have direct membrane effects on the rat MPV.

I. Summary

A large number of drugs affect contractility of the MPV because it possesses nerves, excitable membranes, several ionic channels, and receptors for peptide and other transmitter substances. Interaction with any of these systems can produce effects. Consequently, the calcium antagonist, felodipine, was developed using the MPV as a bioassay. Local anaesthetics excite and then inhibit the MPV. The several prostaglandins can contract or relax the MPV, depending on their chemical structure. They also affect noradrenaline release and, therefore, a number of anti-inflammatory drugs act indirectly to alter noradrenaline release. Morphine can increase frequency of spontaneous contractions and reduce tone; ergometrine acts via α-adrenoceptors; cocaine potentiates the response to noradrenaline. The calcium agonist BAY K 8644 increases vasomotion; chronic treatment with gallopamil lessens the inhibitory effect of reduced extracellular calcium. PAF-acether contracts the MPV and inhibition of this effect has been demonstrated.

Among the peptides, angiotensin II constricts the MPV of most species, whereas vasopressin has little or no effect. Cholecystokinin has inconsistent effects. Bradykinin and substance P contract the MPV, whereas VIP relaxes it. Endothelin is a potent stimulant of contraction of the MPV.

Plasma albumin and γ-globulin increase spontaneous contractility but by different mechanisms, whereas α- and β-globulins are inhibitory.

XI. Pathophysiology

The MPV has been used for a number of studies in which some aspect of its structure, function, or response to drugs under abnormal conditions has been compared with similar aspects under control conditions. The aim has been to try to identify differences between control and experimental tissues and to relate those differences to a particular pathophysiological state.

A. Systemic Hypertension

The MPV from the SHR of the Okamoto strain has been widely used for comparison with control tissue because it is a representative of vascular tissue that is not exposed to the high blood pressure. The nature of the appropriate control animal has been an issue that is not completely resolved but veins from Wistar and/or WKY rats usually have been used. There may be differences in the inbred strains at different times in different parts of the world which adds to the problem of comparisons between results from different laboratories.

Comparison of cyclic AMP levels in the MPV of SHR, Wistar rats, and WKY showed that the values were lower in the SHR compared to the other groups. Furthermore, the values in veins from cross-bred normotensive SHR/WKY did not differ from controls. The levels of cyclic AMP in vessels from young, prehypertensive SHR also were less than in vessels from appropriate control veins (Ramanathan and Shibata, 1974). These observations strongly suggest that the reduced cyclic AMP levels are not caused by the development of the elevated blood pressure in SHR.

Differences have been observed in contractile responses of the SHR compared to control veins, but there has been some inconsistency in the findings of several laboratories. Several groups have observed no difference in the sensitivity to noradrenaline of MPV from SHR compared to Wistar rats (Hallbäck et al., 1971) or WKY (Greenberg and Bohr, 1975). Greenberg and Bohr did observe increased rate and amplitude of spontaneous

contractions, increased maximum response to noradrenaline, and increased sensitivity to prostaglandins A_2 and B_2 in the veins from SHR. Responses to E_2 were decreased, however, and the increased responsiveness to A_2 and B_2 was abolished by indomethacin or by eicotetraynoic acid. It was concluded that the MPV of SHR synthesised more prostaglandins than did veins from WKY (Greenberg, 1976). No actual measurement of rates of synthesis of prostaglandins were reported however. Prostacyclin contracts, rather than relaxes, MPV from both normal rats and SHR to the same extent (Levy, 1978).

The electrical properties of the membrane and the electrical responses to noradrenaline have been compared in the MPV from SHR and WKY (Kuriyama and Suzuki, 1978; Mironneau et al., 1984). No difference was found in the passive electrical properties but noradrenaline depolarised the membrane at 10^{-9} M in the vein of the SHR and at 10^{-8} M in the WKY vein.

Contractility, muscle mass, and sensitivity to agonists was compared in MPVs of SHR, young SHR, and RHR versus MPVs of Wistar rats (Sutter and Ljung, 1977). We observed increased stress in response to noradrenaline and to acetylcholine in the veins of SHR but not in veins of RHR compared to Wistar controls. We also found a decreased ED_{50} for noradrenaline in the veins from SHR in these experiments. When calcium was reduced in the bath fluid, we observed that the MPV from the SHR retained their responses to agonists better than did vessels from normotensive animals. We concluded that the MPV of SHR was functionally different from that of normotensive animals with regard to its handling of calcium. The ED_{50} for serotonin also has been reported to be decreased in MPV of SHR compared to Wistar rats (Ahlund et al., 1977).

Several of these findings were not confirmed when the MPV of 3-month-old SHR was compared with that of 3-month-old WKY (Mulvany et al., 1980). In those experiments neither sensitivity to noradrenaline, maximum force developed, nor cross-sectional area was found to differ in MPV of SHR compared to WKY. In fact Mulvany et al. observed a decrease in stress developed in response to noradrenaline in veins from the SHR compared to control. A possible explanation is that MPVs from WKY were used by the Mulvany group as controls, whereas we had used Wistar rats as the source of control tissue.

Additional experiments have been done to examine the effects of reduced calcium on several aspects of function of the MPV from SHR compared to controls (Pegram and Ljung, 1981). Pegram and Ljung confirmed our earlier findings that veins from SHR sustain their function in lowered external calcium better than control veins (WKY). Responses to agonists and to nerve stimulation were similarly less dependent on or more efficiently used external calcium.

We (Pang and Sutter, 1981) also have found that chronic treatment of SHR with the calcium antagonist gallopamil (D600) exaggerates the ability of the MPV from SHR to sustain their responsiveness in the presence of reduced extracellular calcium. The effect of gallopamil was not due to its ability to lower blood pressure because chronic treatment with hydralazine lacks the ability to exaggerate the responsiveness of veins from SHR in the presence of reduced external calcium (Pang and Sutter, 1980).

The reactivity to calcium in a high potassium medium is increased in MPV from SHR compared to controls but no difference could be detected in the inhibitory effects of the calcium antagonists nifedipine, nitrendipine, or nisoldipine on the two types of vessels (Harris et al., 1984). Similar findings have been made using gallopamil (D600) or felodipine; no differences were observed in the effects of these calcium antagonists on responses of MPV from SHR compared to WKY (Sutter, 1985).

Another group has looked at the contractile effects of angiotensin II on the MPV from SHR and RHR. Couture and Regoli (1980b) found that angiotensin II had increased contractile activity in the veins from SHR but not RHR. The ED_{50} for angiotensin II has been reported to be greater in veins from RHR compared to SHR and WKY. Based on the responses to angiotensin I compared to responses to angiotensin II, the angiotensin-converting enzyme activity seems to be increased in MPV from RHR, but the concentration of captopril required to inhibit conversion of angiotensin I to II was the same in all three strains of rats (Ljung et al., 1981).

In rats made hypertensive by DOCA, it was found that chronic treatment of the animals with indapamide reduced their blood pressure and reduced the frequency of spontaneous contractions in the MPV by 30%. Responses to noradrenaline were not altered by indapamide treatment (Finch et al., 1977). Treatment with hydralazine has been found not to alter the responses to agonists of the MPV from either DOCA-hypertensive rats or SHR, although blood pressure was restored to normal along with responses of the aorta (Pang and Sutter, 1980). We concluded that the aorta is affected by the blood pressure and this is why reduction of pressure alters its contractility. In contrast, others (Greenberg, 1980) have reported that hydralazine, but not minoxidil, reduces the maximum response of the MPV to agonists. The reasons for the discrepant results are not clear but may be due to the problem of appropriate controls in terms of strain, age, and weight of rats.

The turnover of ions has been studied in the MPV of rats with DOCA-hypertension and of normal rabbits. The turnover of ^{42}K was more rapid in the MPV from hypertensive rats than in controls. It also was observed that the rate constants for washout of ^{42}K, ^{36}Cl, and ^{24}Na are greater in MPV of rabbits than in quiescent vessels such as the pulmonary artery (Jones and Miller, 1978).

A number of metabolic measurements have been com-

pared in MPV from SHR and WKY (Arner and Hellstrand, 1981). Arner and Hellstrand found an increased utilisation of oxygen per unit of developed active stress in veins from SHR compared to WKY.

No difference was detected in the presynaptic events in the MPV of SHR compared to normal rats as judged by the ability of β-adrenergic agonists to increase noradrenaline release (Dahlöf et al., 1980). Similarly, no difference was seen in the uptake of noradrenaline in the MPV of SHR compared to the MPV of WKY (Rho et al., 1981). On the other hand, differences have been found in the response of MPV from SHR to transmural stimulation (Westfall et al., 1984). Westfall et al. observed that, in SHR older than 8 weeks, there was increased release of [^{3}H]noradrenaline at low (1–2 Hz) rates of stimulation but not at high (5 or 10 Hz) rates. They also reported that the increased spontaneous contractility in MPV of SHR, which they observed and which had been reported earlier (Greenberg and Bohr, 1975; Sutter and Ljung, 1977), could be reduced by the adrenoceptor antagonist phentolamine.

There is a report of the effects of furosemide, ethacrynic acid, and chlorothiazide on the MPV of SHR compared to WKY (Tayo and Fasanmi, 1984) but the results are difficult to interpret. Furosemide was found to be excitatory and to have a lower ED_{50} in veins from WKY but also a lower maximum effect in WKY compared to SHR. Phenoxybenzamine is reported to inhibit furosemide excitation in SHR but not in WKY. This last finding is indeed puzzling.

Chronic treatment of SHR with the diuretic tienilic acid has been reported to reverse some of the changes observed in MPV from SHR compared to WKY (Mironneau et al., 1984). Specifically, the increased sensitivity of the membrane as measured by its depolarisation in response to noradrenaline, angiotensin II, and prostaglandin E_1, which was observed in veins from SHR, was restored to control values by treatment with tienilic acid.

Relaxin, an ovarian polypeptide hormone, has been reported not to alter the ED_{50} of responses to noradrenaline of MPV from SHR or controls after intravenous infusion for 2 days (Massicotte et al., 1989). In contrast, responses to noradrenaline of the perfused mesentery were blunted (increased ED_{50}) by this treatment. This suggests that the hypotensive effect of relaxin in vivo does not occur via mechanisms operating in the MPV in vitro.

The effects of plasma from patients with essential hypertension on spontaneous contractility and mechanical responses to potassium and noradrenaline have been studied in rat MPV (Pillai and Sutter, 1989). We found that the hypertensive and normotensive plasma prevented responses to noradrenaline and inhibited responses to potassium. The hypertensive plasma was less inhibiting. Plasma from both normotensive and hypertensive patients increased spontaneous contractility, however, and the hypertensive plasma produced a greater increase. These results could be explained if plasma contained both inhibitory and excitatory factors in a proportion that differed in hypertensive patients. Subsequent experiments have provided support for this suggestion (see section IX, H).

B. Portal Hypertension

The effect of hypertrophy of smooth muscle in the MPV has been studied by partial occlusion of the vein near the liver to increase the luminal pressure from 10 to 20 cm of water (Johansson, 1976; 1984). A week to 10 days later the frequency of spontaneous contractions was decreased and the force per contraction was increased in the partially occluded vessel compared to control, sham-operated vessels. Stress developed during the spontaneous contraction as well as that in response to noradrenaline was decreased, however, in the experimental tissue compared to control. The ED_{50} for noradrenaline also was increased in hypertrophied vessels.

The reduction of spontaneous activity that occurs in ligated, hypertrophied MPV has been confirmed. When normalised for weight, the oxygen consumption and lactic acid production also are reported to be increased in hypertrophied veins (Arner and Uvelius, 1981). Dose-response curves to increasing concentrations of calcium were not different in either intact or chemically skinned hypertrophied MPV compared to controls. There was a difference in the rate of development of tension, however (Arner et al., 1985). Arner et al. suggested that this is due to a low rate of cross-bridge turnover in hypertrophied veins.

The production of prostacyclin has been reported to be increased compared to controls in MPV from rats with portal hypertension (Hamilton et al., 1981; 1982). It was suggested that this may contribute to the development of oesophageal varices in cirrhosis. The MPVs from rats with portal hypertension are reported to be 3–10 times more sensitive to serotonin compared to control veins (Cummings et al., 1986). Ketanserin competitively antagonised serotonin in these veins.

Electron microscopy has been done on hypertrophied rabbit MPV and has revealed that the number of intermediate filaments is increased (Berner et al., 1981). The ratio of actin to intermediate to myosin filaments in hypertrophied muscle cells was 15:3.5:0.5 compared to 15:1.1:1 in controls. Electron probe analysis of rabbit MPV could detect no difference in the sodium, potassium, chloride, magnesium, calcium, phosphorus, or sulphur content of hypertrophied veins compared to controls (Junker et al., 1984).

A correlation has been suggested between the contractile responses of the MPV and the survival of dogs with their portal veins ligated (Fujii et al., 1988). This was based on the observation that the MPV of dogs that died had less spontaneous contractility and reduced responses

to potassium, noradrenaline, acetylcholine, and histamine compared to veins from dogs that survived.

Rats have been made cirrhotic by repeated injections of CCl_4 and the perfused MPV from such animals was compared with veins from control rats (Yoshimura et al., 1988). It was found that spontaneously developed stress was greater per contraction in the veins from the treated animals but the frequency of spontaneous contractions was less. Reduction of external calcium also seemed to have less effect on spontaneous and noradrenaline-induced contractions in the veins from cirrhotic animals. Yoshimura et al. suggested that this increased responsiveness may play a role in the elevated portal pressure seen in cirrhosis.

C. Diabetes and Thyroid

Several investigators have studied the MPV from rats or other animals made diabetic by treatment with either alloxan or streptozotocin. In one of the early studies alloxan was used and the responses of perfused MPV from alloxan-treated rats was compared with those from normal and starved rats (Fiol de Cuneo et al., 1980). Responses of both starved and alloxan-treated veins were reduced compared to controls but did not differ one from the other. Insulin added to the bathing fluid improved the contractility of veins from diabetic, but not starved, animals.

In another study in which alloxan was used no difference was found in the calcium kinetics of MPV from diabetic animals compared to controls (Turlapaty et al., 1980). Spontaneous contractility was greater in the MPV of the alloxan-treated animals, however.

Spiral strips of MPV from rats treated with streptozotocin were compared with strips from control animals and no differences were found in responses to noradrenaline, serotonin, or potassium (MacLeod and McNeill, 1985).

Hypothyroidism produced by treatment of rats with methimazole had no effect on adrenoceptor function in rat MPV (Yoong et al., 1982). Dose-response curves to noradrenaline and to angiotensin were not different in hypothyroid animals and inhibition produced by phentolamine or propranolol to their selective agonists did not differ in veins from the treated rats.

D. Miscellaneous

The MPV from germ-free rats has been shown to have decreased responses to noradrenaline and angiotensin both in terms of increased ED_{50} and decreased maximum contraction. Responses to $CaCl_2$ were decreased but those to KCl were not. This pattern differed from that seen in aortas from the same animals (Altura et al., 1975).

Gram-negative endotoxins have been studied on guinea pig MPV and found to have no effect on electrical events measured by sucrose-gap electrode and found not to alter responses to noradrenaline or transmural nerve stimulation (McLean, 1978).

In dystrophic hamsters the contractile response of the MPV to transmural stimulation of noradrenergic nerves or to noradrenaline was similar to those of nondystrophic hamsters (Bennett and Gardiner, 1977).

Angiotensin II apparently has an increased pressor response in nephrectomised animals. Therefore, the sensitivity to angiotensin II and to noradrenaline was examined in the MPV of nephrectomised rats 24–48 h after surgery and in the MPV of rats subjected to surgery only 2 h previously. It was found that sensitivity to each of these agents was the same in experimental and control tissues (Couture et al., 1978). Sodium restriction was found to alter the indirect (via released noradrenaline) responses of the rabbit MPV to angiotensin (Sybertz and Peach, 1980). The ability of angiotensin II or III to potentiate the contractile response to transmural electrical stimulation was decreased by sodium restriction, presumably because of altered release of noradrenaline. Similar findings have been made in MPV from SHR and WKY (Westfall et al., 1985).

The effects of ageing and of uninephrectomy were studied on the responses to angiotensin II in MPV from rats (Couture and Regoli, 1980a). Neither condition affected the responses to this agent. Ageing similarly was found not to affect the ability of atrial naturetic peptide (AP-25) to relax the MPV (Emmick and Cohen, 1986).

Increased hydrostatic pressure has been reported to affect the MPV (Sigurdsson and Ornhagen, 1980). Spontaneous activity increased during the elevation of atmospheric pressure and decreased when the high pressure had stabilised. At a pressure of 100 atm, frequency was reduced by approximately 46% and integrated tension by 40%, whereas responses to electrical stimulation were reduced by 44% and responses to potassium were reduced by 15%. Decompression further decreased spontaneous contractility but the changes were reversible after hydrostatic pressure returned to normal.

Ligation of the bile duct has been reported to reduce the responsiveness of the rat MPV to noradrenaline or tyramine (Bomzon et al., 1984). Addition of some, but not all, types of bile salts to the bath also could reduce the responses of the vein. Bomzon et al. wondered whether the inhibitory effects of bile salts could explain the mechanism of hypotension seen in some patients with obstructive jaundice. There seems to be an effect of time after ligation. Maximum contractions were reduced in veins from ligated animals 3 and 6 days after surgery, but the ED_{50} for noradrenaline was reduced only at 3 days (Bomzon et al., 1985).

E. Summary

Comparisons have been made of the MPV of the SHR versus controls and the results are not always consistent. The following differences seem to exist in the MPV of SHR: decreased cyclic AMP, increased depolarisation in

response to noradrenaline, increased sensitivity to serotonin, increased spontaneous contractility, and less dependence on external calcium. In MPV from DOCA-hypertensive rats few differences from control have been found, although there may be increased ionic flux in such vessels.

In MPV made hypertrophic by partial occlusion of the portal vein, decreased spontaneous activity and decreased active stress have been observed. The histological and subcellular changes in these vessels have been described. Different functional changes occur when portal hypertension is produced by CCl_4-induced cirrhosis rather than ligation.

Diabetes produced by alloxan is accompanied by functional changes in the MPV that seem related to starvation. Streptozotocin-induced diabetes or hyperthyroidism produced by methimazole has little or no effect on the MPV.

Gram-negative endotoxins and ageing have no effect on the MPV. Increased hydrostatic pressure or bile duct ligation decreases spontaneous contractility and sodium restriction alters the interaction of angiotensin II with noradrenergic nerves in the MPV.

XII. Conclusions

The MPV has proven to be a versatile tissue for the study of vascular and smooth muscle structure and function and for the study of drugs. The fact that felodipine was developed using the MPV as a model of the resistance vasculature suggests that the basic physiology of the MPV indeed resembles the peripheral vasculature. Much is known about the structure, pharmacology, physiology, and biochemistry of the MPV but several questions remain. In particular, we need a coherent understanding of the dynamic aspects of excitation, E-C coupling, contraction, and relaxation. At present we have only pieces of the puzzle. Perhaps study of the MPV in a comprehensive fashion will add to our understanding of vascular smooth muscle and enable us ultimately to describe the sequence and control of events that alter the calibre of blood vessels.

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