CHAPTER 1

GENERAL REVIEW OF THE LITERATURE

Introduction

The fresh and dried fruits from the plant genus Capsicum, commonly known as hot pepper or chili, are among the most heavily consumed food additives. Peoples in different parts of the world, particularly those in Asia, Central and Latin America, and Africa, use hot pepper as spice apparently to make the food tasty and to stimulate appetite. The principal pungent constitutent largely responsible for this flavor enhancement is a substance called capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide). Capsicum fruits contain approximately 0.1-1.0 % capsaicin (Sirsat and Khanolkar, 1960). Capsaicin is a relatively simple and low molecular weight substance, the structure of which is shown in Fig. 1. Being a stable compound, capsaicin evidently persists in dried pepper with unchanged potency (Nelson and Dawson, 1923), and concentration as low as 10 ppm can be detected by tasting. It has been estimated that in some South East Asian countries average daily per capita intake of hot pepper may be as high as 5 gm or about 50 mg of capsaicin (Buck and Burks, 1983). Capsaicin is sparingly miscible with cold water but freely soluble in hot water and many organic solvents including alcohol, ether and chloroform. The chemical melts at 63°-65° C, and at higher temperature is volatile producing extremely irritating vapor (Strecher, 1968).

To many investigators, capsaicin's pungency and algesic activity has long captured their attention since it suggests the chemical should possess biological actions. Indeed, numerous studies over the past several decades have revealed surprisingly diverse effects of capsaicin on many physiological systems. For instance, thermoregulation, gastrointestinal tract, sensory nerve, cardiovascular and respiratory system have all been demonstrated to be affected by capsaicin. Furthermore, capsaicin also has cytotoxic activity, i.e, the agent can cause several subcellular structural damages, notably those of the mitochondria (Virus and Gebhart, 1979). Pharmacologic interest in capsaicin has grown steadily over the years and, most recently, has been intensified by the discovery that capsaicin is a substance P- depleting agent. This finding makes capsaicin a potentially valuable new pharmacological tool to probe the functions of substance P-containing neurons (Buck and Burks, 1983). Obviously, the literature on the biological actions of capsaicin is quite voluminous, which precludes comprehensive review of the subject in this thesis. Thus, in the following sections, only the relevant cardiovascular effect of capsaicin is described in some details while rather brief accounts on other aspects of capsaicin pharmacology are presented.

Capsaicin and Thermoregulation

Among its diverse biological actions, capsaicin has profound effect on body temperature regulation in experimental animals. Early study by Issekutz et al. (1950) demonstrated the hypothermic effect following subcutaneous capsaicin administration to the mice. Similar effect was observed after histamine administration. However, the

hypothermia induced by capsaicin and by histamine apparently has different mechanism of actions since the former did not change metabolic rate while the latter produced a decrease. Later investigations by Jancso-Gabor et al. (1970 a, b) has confirmed and extended this result. They found that rats injected subcutaneously with capsaicin developed hypothermia associated with skin vasodilation. After repeated injections the hypothermic response diminished and finally disappeared. Such desensitized animals lost the ability to regulate their body temperature in high ambient temperature, they responded to high temperature environments with hyperthermia. On the otherhand, temperature regulation against cold was normal. Impairment of heat dissipating mechanism (e.g., salivation) rather than increased heat production appeared responsible for the hyperthermic response. These authors suggested that the hypothermic effect elicited by acute capsaicin administration was due to stimulation of the hypothalamic warmth receptors followed by receptor desensitization after chronic treatment or high doses of capsaicin. This suggestion was supported by further experiments in which capsaicin was injected directly into the brain. Injection of capsaicin into the hypothalamic preoptic area of the rats produced a prompt decline in body temperature very similar to that observed after peripheral capsaicin administration, and, likewise, repeated injections caused desensitization. Histological examination of the preoptic area from capsaicin-desensitized rats did not unveil any cell destruction. However, electron microscopic study revealed ultrastructural changes, particularly the swollen mitochondria, in only one type of preoptic neurons characterized by relatively small cell size and profuse rough endoplasmic reticulum. The authors then correlated this subcellular changes with functional alterations and postulated

that the neurons in the preoptic area with swollen mitochondria after capsaicin desensitization are the hypothalamic warmth detectors (Szolcsanyi et al., 1971). It is noteworthy that the neuronal ultrastructural changes is amazingly long-lasting and may persist several months after capsaicin treatment.

The above studies, although clearly demonstrate the ability of capsaicin to influence thermoregulatory process, do not disclose any information concerning the molecular mechanism of action. Since C-AMP has been implicated a significant role in hypothalamic regulatory functions including central thermoregulation (Breckenridge and lisk, 1969., Laburn et al., 1974), Jancso-Gabor and Wollemann (1976) have investigated whether capsaicin has any effect on the adenyl cyclase activity in different regions of rat brain. In rats desensitized by subcutaneous capsaicin injections, the basal adenyl cyclase activity of the preoptic area was found increased as much as tenfold compared with control animals whereas the enzyme activity of cerebellum and parietal cortex was unchanged or slightly decreased. The authors proposed that the increased adenyl cyclase activity may, at least partly, be the mechanism responsible for the capsaicin-induced derangement in thermoregulation.

Capsaicin and Gastrointestinal Functions.

The hot burning taste and pain-producing property of capsaicin ostensibly has led several investigators to conjecture the possible connection between hot pepper consumption and gastrointestinal disturbances. Viranuwatti et al. (1972) have studied the direct local effect of capsicum solution on human surface gastric mucosa by visual observation through gastroscope. Of the twenty human subjects receiving

3 % capsicum solution instilled through intragastric tube or gastrofiberscope lumen, three cases mildly responded with mucosal edema and/or hyperemia. Other three developed moderate reactions of multiple hemorrhagic spots. Only one case severely responded with massive bleeding areas followed by hematemesis during the examination. No relationship was found between abnormal gastroscopic findings and the amount of capsicum consumed habitually. These authors suggested that the capsicum-induced increase in gastric acid secretion (Ketusinh et al., 1966) together with capsicum's irritating activity can cause gastric mucosal cells damages leading to hemorrhagic gastritis as well as deterioration of ulcer symptoms. They also contended that capsicum should be excluded from diets of ulcer and gastritis patients.

Although Toh et al. (1955) found no effect of capsaicin on gastric acid secretion in the cats, other studies with different laboratory animals definitely have shown the stimulatory action of capsaicin and capsicum extract on gastric acid output. Lille and Ramirez (1935) reported small increase in gastric acid secretion after capsicum extract was injected intravenously into the dogs. Kolatat and Chungchareon (1972) found capsicum solution to enhance gastric motility and increased blood flow through superior mesenteric artery and gastric mucosa in rats, guinea pigs, and dogs. Interrupting the vagus nerve did not whereas atropine pretreatment abolish these effects. It was concluded that capsicum directly stimulated gastrointestinal parasympathetic nerve causing an increase in gastric motility and, consequently, gastric mucosal blood flow and acid output. Recent study by Limlomwongse et al. (1979) on gastric acid output and mucosal blood flow in the rats suggested that capsaicin induced the release of endogenous gastric secretagogues such as acetylcholine and histamine which enhanced gastric

mucosal blood flow and, therefore, acid secretion.

The cytotoxic activity of capsaicin on gastrointestinal tract has been strikingly demonstrated by Nopanitaya and Nye (1974). Intraduodenal or intragastric administration of natural or synthetic capsaicin to the rats was found to produce structural damages to duodenal absorptive cells. Cell injury can be detected within 2 minutes after exposure to capsaicin, with maximum damages in 45 minutes. Electron microscopic examinations showed swollen mitochondria with rarefied matrix and disorganized cristae. Nuclei were shrunken and chromatin was clumped and marginated at the nuclear envelope. In addition, increased number of free ribosomes and lysosomes as well as dilatation of endoplasmic reticulum and Golgi complexes were also observed. These structural alterations evidently imply functional disturbances. In fact, Monsereenusorn and Glinsukon (1978) later demonstrated impairment of intestinal absorptive capacity by capsaicin and capsicum extract. Employing rat and hamster intestine in vitro, these investigators showed the impaired intestinal glucose absorption induced by capsaicin at 14 mg/100ml. The degree of inhibition was dependent on both capsaicin concentration and incubation time, the relationship between the latter and diminished glucose absorption being linear. The decrease in intestinal ATP content most likely accounted for the reduced glucose transport. Since 100 µM ATP added to the mucosal side of capsaicin-treated intestine restored glucose absorption to control value. Actual ATP measurements revealed 17 % and 36 % reduction in ATP level of capsaicin-treated rat and hamster jejunum respectively. The authors commented that the active transport of other nutrients, for instance amino acids, should be similarly affected by capsaicin. In this connection, it is pertinent to note that Nopanitaya (1973) has reported the significant

decrease in fat absorption and growth rate in rats fed diet with capsaicin as compared to control animals on same diet without capsaicin. Inasmuch as hot pepper is a common dietary ingredient consumed by people throughout the world, these findings have obvious significant nutritional consequences. However, whether these effects of capsaicin are applicable to man remains to be investigated.

The reported abnormal mitochondrial morphology in certain preoptic neurons and duodenal mucosal cells following capsaicin administration described above has led Chudapongse and Janthasoot (1976, 1981) to investigate capsaicin effect on mitochondrial energy-linked functions. Capsaicin was found to inhibit the response of isolated rat liver mitochondria to the additions of ADP, DNP, and $CaCl_2$. This inhibition was partially reversed by adding bovine serum albumin to the medium. Interference with electron transfer from NADH to coenzyme Q in mitochondrial respiratory chain was found to be the mechanism of capsaicin action on the mitochondria. Thus, these studies clearly indicate direct toxic effect of capsaicin on mitochondrial energy metabolism. It is very likely that the decrease in ATP levels of capsaicin-treated rat and hamster intestine mentioned above arises from capsaicin action on intestinal mitochondria. Moreover, the inhibition of mitochondrial oxidative phosphorylation may be a contributing factor to the pathogenesis of hepatic cirrhosis found in rabbits receiving high-fat or high-carbohydrate diets supplemented with red pepper (Lee, 1963).

Capsaicin has long been known to enhance gastrointestinal movements. Very low concentration (0.1 µg/ml) has been shown to induce contraction of isolated guinea pig ileum (Molnar et al. , 1969). However, tachyphylaxis highly specific to capsaicin rapidly ensued. No

cross-tachyphylaxis to acetylcholine, histamine, serotonin, nicotine, bradykinin, KCl, and $BaCl_2$ was observed. Experiments with pharmacological antagonists of several receptor types excluded cholinergic, histamine and serotonin receptors from being involved in the capsaicin-mediated ileum contraction. More recent studies suggested the participation of sensory nerve since in vivo denervation of the ileum inhibited contractile response to capsaicin, and stimulation of the mesenteric periarterial sensory nerve produced contractions indistinguishable from those produced by capsaicin (Bartho and Szolcsanyi, 1978; Szolcsanyi and Bartho, 1978).

Sensory Effect of Capsaicin

The irritation and pain sensation following topical application of capsaicin to skin and mucous membrane is well known. Capsaicin applied repeatedly to skin of adult animals was found to produce initial irritation which progressed to long-lasting insensitivity to most chemical irritants while responses to light touch and mechanical stimulation were unimpaired (Virus and Gebhart, 1979; Nagy, 1982). Similar desensitization can also be induced by parenteral administration of capsaicin at high doses. Earlier neuroanatomical study showed that in desensitized rats the small type B spinal neurons displayed ultrastructural changes, particularly the mitochondrial swelling (Joo et al., 1969). These changes resemble those found in certain preoptic neurons after thermal desensitization evoked by capsaicin (Szolcsanyi et al, 1971). Subsequent investigations have suggested relationship between the initial release followed by depletion of substance P in primary sensory fibers and the capsaicin-mediated sensory aberrations (Nagy,

1982; Buck and Burks, 1983). Substance P, the undecapeptide, is a neuropeptide believed to play a role as neurotransmitter or neuromodulator in certain small unmyelinated sensory neurons (type C) mediating the transduction of nociceptive stimuli. Capsaicin treatment in adult animals can cause substance P depletion as much as 85 % in the dorsal root ganglia. It is very interesting to note that the substance P-depleting action of capsaicin is strictly confined to the sensory neurons since sympathetic or parasympathetic neurons or neurons in the brain, except some in the preoptic region, are not affected by capsaicin administration.

Gamse and collaborators (1979) studied the effect of capsaicin on substance P release from spinal cord and hypothalamic slices. They found that capsaicin produced a dose-dependent release of substance P from spinal cord but not from hypothalamic slices. This effect exhibited calcium dependency because it can be obliterated by adding EGTA which removed extracellular calcium. On the other hand tetrodotoxin, a specific sodium channel blocker, failed to reduce capsaicin effect on substance P release, indicating that capsaicin acted directly without requiring rapid sodium entry. Since the unmyelinated primary afferent neurons are the major substance P-containing sensory nerves in spinal cord, it is very reasonable to assume that the capsaicin-induced substance P release originated from these pain fibers. Since hypothalamic slices was found unresponsive to capsaicin, the involvement of hypothalamic substance P in thermal desensitization caused by capsaicin appeared unlikely.

Capsaicin administered to newborn rats causes extensive degeneration of primary afferent neurons. Adult animals given capsaicin neonatally have reduced number of sensory ganglia neurons and their fibers. This deleterious action does not occur with adult animals given capsaicin

(Nagy, 1982). Mayer et al. (1980) have studied the effect of capsaicin pretreatment on substance P binding to synaptic vesicles from both adult and neonatal rats. They found that, in both groups, pretreatment with capsaicin led to a significant reduction in the number of binding sites on vesicles prepared from dorsal root ganglia and spinal cord. No change in the affinity was observed. This decrease was found paralleled to the depletion of substance P content (Gamse et al., 1980). Recent report, however, showed the inhibitory effect of capsaicin on axonal transport of substance P when the chemical was applied locally to peripheral nerves (Nagy, 1982). Thus, it is still far from clear how capsaicin brings about substance P depletion in the sensory neural elements.

In an attempt to correlate capsaicin molecular structure with its pharmacologic activity, Szolcsanyi and Jancso- Gabor (1975,1976) compared the pain-producing potency and desensitizing activity of capsaicin with several congeners. They found that these two actions had different structural requirements. For algesic activity the requirements are as follows: a free hydroxyl group on aromatic ring is essential; a critical distance linking the acylamide and vanillyl group must be maintained; and the alkyl chain has an optimal length of 8-10 carbon atoms. On the contrary, the desensitizing potency requires acylamide structure and optimal alkyl chain length appears to be 10-12 carbon atoms. While nociceptive potency is retained by substitution of the acylamide with alkyl ester moiety, this structural modification abolishes desensitizing activity. Thus capsaicin appears to produce its effects by interacting with distinct molecular recognition site(s) which is able to discriminate subtle changes in ligand structure. However, efforts in several laboratories to show receptor binding with radiolabeled capsaicin

analogs have so far been unsuccessful (Buck and Burks, 1983). Even if such "capsaicin receptor" can eventually be demonstrated and characterized, it remains dubious whether all the diverse biological actions of this compound result from the capsaicin-receptor interaction. These enigmatic problems of capsaicin pharmacology certainly deserve vigorous investigation in the near future.

Capsaicin and Cardiovascular System

The action of capsaicin on the cardiovascular system is now well-documented. This compound produces variable effects on cardiovascular functions. Most investigations in this area have been carried out with intact animals and only few reports concerning in vitro effect on isolated tissue preparations appear in the literature. In the mid 1930s. Lille and Ramirez suggested a potent hypotensive effect exerted by capsaicin in anesthetized dogs. Two decades later, Toh et al. (1955) and Porszasz and coworkers (1955, 1957) studied the effect of capsaicin given intravenously in anesthetized cats and dogs. The Bezold-Jarisch reflex (hypotension, bradycardia, and apnea) was observed after capsaicin administration. In both species the apnea was followed by an increased respiratory rate. Tachyphylaxis to repeated intravenous administration of capsaicin during the 2-3 hours period could not be demonstrated in these studies. Capsaicin was found to be most efficacious in eliciting the Bezold-Jarisch reflex when injected directly into the bifurcation of pulmonary artery. These cardiovascular and respiratory responses were abolished by vagal cooling or vagotomy, sugggesting that vagal reflexes mediated these responses. The hypotension evoked by intravenous capsaicin was attributed to the stimulation or sensitization

of carotid sinus bororeceptors since sectioning sinus nerve or cocaine applied directly to carotid sinuses completely obliterated the hypotensive effect. In agreement with this conclusion, Coleridge et al. (1964) recorded action potentials from baroreceptor afferents in vagus nerve and found that some of the baroreceptor fibers were activated or sensitized by capsaicin. In addition, capsaicin injected directly into pulmonary artery was found to produce effects very similar to those elicited by intravenous injection, suggesting involvement of receptors in the pulmonary vascular bed, as well as arterial baroreceptors, in the cardiovascular and respiratory effects of capsaicin. Thus, these results have provided strong evidence for the reflex cardiovascular changes produced by capsaicin. By sensitizing baroreceptors in the carotid sinuses and receptors in the pulmonary circulation, the chemical causes an increase in afferent vagal discharge resulting in reflex hypotension and bradycardia. Makara et al. (1967) examined the effect of chronic capsaicin treatment on the cardiovascular responses to intravenous capsaicin, serotonin, and histamine in the rats. Capsaicin pretreatment was found to inhibit the hypotensive effect of subsequent intravenous capsaicin, to attenuate the hypotensive response to serotonin, and to have no influence on the histamine-mediated hypotension. These authors suggested that serotonin may play some role in the cardiovascular action of capsaicin

More recently, Toda et al. (1972) have compared cardiovascular effect of capsaicin in anesthetized dogs and rabbits. Capsaicin (10-300 µg/kg) was found to cause a transient rise in mean systemic blood pressure followed by a sustained fall in the dogs, whereas only hypotension was observed in the rabbits. The hypotension in dogs and rabbits was diminished by atropine, suggesting the involvement of cholinergic

mechanism, most likely the vagi. The increased blood pressure observed in the dogs was not influenced by hexamethonium, tolazoline and phentolamine. In the atropine-treated dogs the heart rate was not altered or was slightly increased by capsaicin despite a marked rise in blood pressure. The rate and contractile force of isolated dog and rabbit atria did not change significantly by capsaicin (0.02-2 µg/ml). However, capsaicin caused a sustained increase in the tension of spiral strip from proximal and distal mesenteric arteries and proximal and distal renal arteries of the dog. The tension increment was not significantly altered by phentolamine; but decreasing extracellular calcium ion to one-third of normal value reduced the contractile effect of capsaicin on dog superior mesenteric arteries. The authors concluded that in the dogs, capsaicin directly exerted its hypertensive action by causing vasoconstriction of peripheral vasculature without affecting cardiac function. And the capsaicin-induced, non-reflex vasoconstriction was intimately related to the extracellular calcium ion not to an adrenergic mechanism.

Although Toda and coworkers (1972) failed to demonstrate capsaicin effect on isolated atria from dog and rabbit, previous study by Molnar et al. (1969) has shown stimulatory effect of this compound on isolated guinea pig atria. Capsaicin at concentrations from 0.05 to 0.1 µg/ml was found to produce positive inotropic and chronotropic effect. However, a prolonged and highly specific tachyphylaxis to capsaicin rapidly ensued. The capsaicin-desensitized atria still retained their responsiveness to catecholamines, tyramine and nicotine. Neither propranolol nor cocaine could antagonize the positive inotropic and chronotropic effect of capsaicin on isolated guinea pig auricles, suggesting that this effect did not involve the release of endogenous catecholamines.

Capsaicin has been demonstrated by several investigators to evoke reflex changes in cardiovascular functions when this compound is injected into local circulation supplying certain organs in laboratory animals. Capsaicin can reflexly mediate either cardiovascular stimulation or depression depending on which organ has received the chemical. In 1972, Webb-Peploe et al. reported several reflex cardiovascular adjustments including: increases in blood pressure and vascular resistence in the hind limb, gut, and kidney following infusion of capsaicin into the dog femoral artery. The authors suggested that the capsaicin-sensitive receptors in skeletal muscle may be activated during muscular contraction to reflexly cause a redistribution of blood flow. Subsequent study by Crayton and collaborators (1981) has confirmed and extended this result. In anesthetized dogs, capsaicin (1-10 μg/kg) injected into the arterial blood supply to the neurally intact donor-perfused hindlimb was found to produce significant increases in mean aortic pressure, heart rate, cardiac output, and respiratory minute volume. Organ blood flow measurements during capsaicin injection revealed a decrease in renal blood flow, but flows in liver, spleen, brain, heart, and skeletal muscles remained near control values. These changes resemble those induced by isometric exercise in the dogs (Crayton et al., 1979) and the cats (Coote et al., 1971) ; Mitchell et al., 1977). After sectioning the femoral and sciatic nerves these cardiovascular and respiratory responses to capsaicin infusion were abolished, indicating the involvement of the reflex mechanism. Because skinning the experimental hindlimb and occluding paw blood flow did not attenuate the responses to capsaicin, cutaneous receptors appeared unlikely to involve. likewise, bones and joints probably not participated since intra-arterial capsaicin injection into an isolated gracilis muscle evoked reflex changes similar to those

seen with capsaicin infusion into the entire leg. The authors suggested that the capsaicin-sensitive receptors most probably located in or in proximity to the muscle. Kaufman et al. (1982) have attempted to identify electrophysiologically which afferent fibers are stimulated by capsaicin by recording impulse activity from afferent nerves with endings in either the gastrocnemius or gracilis muscles in anesthetized dogs. Capsaicin (10-30 μg/kg) injected into the abdominal aorta was found to stimulate 24 of 34 group IV (C fiber) endings, but only 5 of 19 group III (A σfiber) endings. Impulses from the 24 group IV afferents stimulated by capsaicin increased from the average 0.7 to a peak of 9.3 impulses/sec. These responses were not tachyphylactic. Capsaicin had no significant effect on the firing rate of 30 group I and II muscle afferents. Similar experiment with bradykinin, an algesic substance (Guzman et al., 1962) known to stimulate group III and IV muscle afferents (Kumazawa and Mizumura, 1977), showed that bradykinin (0.5-1.5 μg/kg) stimulated 17 of 33 group IV endings and 9 of 19 group III endings. Thus capsaicin was found more specific than bradykinin on group IV muscle afferents. These results indicated that the reflex increases in cardiovascular functions evoked hindlimb were mediated primarily through group IV muscle afferents. The capsaicin's unique capability to specifically stimulate group IV muscle endings confers potential pharmacologic usefulness as a tool to determine the reflex autonomic effects resulting from stimulating group IV muscle afferents. In addition, this compound may be valuable in determining the connections of group IV muscle afferents to sites in the central nervous system involved in cardiovascular control.

Longhurst and collaborators (1980), utilizing the C-fiber agonistic action of capsaicin, have demonstrated the potential role of the stomach as a reflexogenic organ which regulates the cardiovascular functions. In this study, they developed the autoperfused stomach preparations in anesthetized dogs so that capasaicin could be injected into the left gastroepiploic artery supplying the greater curvature of the stomach. Control injections were made into the inferior vena cava to determine capsaicin effect on areas downstream from the stomach. Capsaicin (25-500 µg) caused significant increases in systolic blood pressure, heart rate, contractility, and systemic vascular resistance but no changes in aortic flow and left ventricular end-diastolic pressure. On the other hand, downstream vena caval capsaicin injection evoked significant decreases in systolic blood pressure, heart rate, contractility, and aortic flow without changing the systemic vascular resistance or left ventricular end-diastolic pressure. The responses of pressure, rate, and contractility induced by intra-arterial gastric injections were diminished to a large extent by diaphragmatic celiac nerve section (sympathetic) and to a smaller extent by diaphragmatic vagus nerve severance (parasympathetic). The opposite nature of the cardiovascular responses to gastric and vena caval capsaicin injections as well as the result of nerve section suggested the reflexes were limited to the stomach or its adjacent regions. The relative importance of the parasympathetic pathway cannot be determined with certainty in these experiments since thoracic sympathetic fibers are known to mix with the thoracic vagus nerve for some distance above the diaphragm. These authors attributed the capsaicin-induced cardiovascular stimulation to the activation of C-fiber afferent endings in the stomach or nearby

locations.

Most recently, reflex cardiovascular changes induced by localized capsaicin injection into canine liver have been reported by Ashton et al. (1982). These investigators developed an animal model in which the venous return from the inferior vena cava was discarded while total venous return to the right heart was mantained constant. This model allowed capsaicin to be injected into the portal circulation of the liver but systemic circulation of the drug was prevented. Capsaicin (500 μg) was found to rapidly decreased left ventricular systolic pressure, mean arterial pressure, heart rate, contractility, and renal vascular resistance. Left ventricular end-diastolic pressure did not change. Interrupting the vagus nerve at the level of diaphragm did not alter hemodynamic changes occurring during capsaicin injections, but anterior hepatic nerve section eliminated the changes, indicating the cardiovascular responses were reflex in origin. The authors concluded that liver tissue contained capsaicin-sensitive afferent endings, most likely type C fibers, activation of which induced reflex cardiovascular depression. And this pathway may importantly contribute to the overall regulation of the cordiovascular functions.

The cellular mechanism of capsaicin action on the cardiovascular system is still obscure at present. Increased activity of the small unmyelinated fibers (type C) appears to play a major role in the reflex cardiovascular alterations evoked by capsaicin administration. Several lines of experimental evidence suggest that the cardiovascular and nociceptive effects of capsaicin may be related to the putative undecapeptide neurotransmitter substance P. Substance P has been localized in primary sensory neurons (Otsuka and Konishi, 1977), spinal cord dorsal horn (Chan-Ralay and Palay, 1977) vagal baroreceptor afferents

(Gamse et al., 1980), the nucleus tractus solitarius (Cuello and McQueen, 1980), sympathetic ganglia, and adrenal medullary paraneurons (Hokfelt et al, 1977 ; Livett et al., 1979). Capsaicin has been shown to cause the release and/or depletion of substance P in both peripheral and central nervous system (Jessell et al., 1979 ; Yaksh et al., 1979 ; Gamse et al., 1980). However, if capsaicin produces reflex cardiovascular changes through substance P release, tachyphylaxis to repeated capsaicin administration is to be expected. Most cardiovascular responses reflexly mediated by capsaicin, on the otherhand, are not tachyphylactic. This point must be clarified before the effect of capsaicin on substance P can be causally related to its cardiovascular action

To recapitulate, capsaicin has been shown to produce marked effects in a wide range of physiological systems. In several instances, acute initial effects are followed by desensitization or tachyphylaxis. Considerable evidence indicates that certain physiologic actions of capsaicin may, at least partly, involve substance P release and/or depletion. Regarding the cardiovascular system, capsaicin can induce either reflex cardiovascular stimulation or inhibition depending on the site of drug administration. Limited in vitro studies have demonstrated stimulatory action of capsaicin on isolated atria and vascular smooth muscle.