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REVIEW ARTICLE

PELARGONIC ACID VANILYLLAMIDE (PAVA): RIOT CONTROL AGENT

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Summary

Riot control agents are highly potent sensory irritants of relatively low toxicity that produce dose and time-dependent acute site-specific toxicity. These compounds have been referred to as transient incapacitating agents or as lacrimators, and in common parlance they are known as "tear gases". These compounds interact pharmacologically with sensory nerve receptors associated with mucosal surfaces and the skin at the site of contamination, resulting in localized discomfort or pain with associated reflexes. This biological response, e.g. ocular irritation, results in pain in the eye and excess reflex lacrimation and blepharospasm. Riot control agents have both civil and military applications and have been classified as either military chemicals or chemical warfare agents. Non-lethal or less lethal weapons have become increasingly popular for law enforcement use when confronting dangerous, combative individuals in the field, include riot control agents. Many incapacitating agents were developed during the Cold War. Oleoresin capsicum (OC) spray, an extracted resin from *Capsicum* pepper plants, was first developed in the 1970s as an alternative to CS (2-chlorobenzylidene malononitrile) and CN (chloroacetophenone) agents. Most recently, a synthetic form of capsaicin, PAVA (pelargonic acid vanillylamide), gained popularity as a defensive aerosol in the early 1990s. Chemical, pharmacological, and toxicological properties of PAVA are discussed in this paper.

Key words: Riot control agents; capsacinoids; pelargonic acid vanillylamide; vanilloid receptors; chemistry; pharmacology; toxicology; risk assessment.

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INTRODUCTION

Riot control agents (RCA) are non-lethal lachrymatory or transient incapacitating agents used for riot control (Beswick, 1983). Although the two classes share the characteristic to incapacitate, a distinction must be drawn between these two types

of agents. RCAs differ from incapacitating agents in several respects. RCA possess a relatively short onset and limited duration of action (Olajos and Salem, 2001). They can rapidly produce sensory irritation or disabling physical effects which usually disappear within minutes and up to hours following termination of exposure (Hilmas et al., 2009). Most commonly used RCA are pepper spray and various kinds of tear gases. These chemicals disperse a crowd that could be protesting or rioting, or to clear a building. They can also be used for chemical warfare defense training (Huntington and Gavagan, 2011), although their use in warfare itself is a violation of Article I.5 of the Chemical Weapons Convention (CWC). Article II.9 of the CWC specifically authorizes their use for civilian law enforcement. The active ingredient in pepper spray is capsaicin, which is a chemical derived from the fruit of plants in the *Capsicum* genus. A synthetic analogue of capsaicin, pelargonic acid vanillylamide, is used in another version of pepper spray known as PAVA (pelargonic acid vanillylamide) spray which is used e.g. in England. Toxicological profile for PAVA and health risk assesment of this compound are discused in this article.

HISTORY

Probably first RCAs were used during the 5th century BC Peloponnesian War when the Spartans used smoke from burning coal, sulfur, and pitch to temporarily incapacitate and confuse occupants of Athenian strongholds (Horká, 2007). During antiquity, the Romans used irritant clouds to drive out their Spanish adversaries from hidden dwellings (Robinson, 1971). Almost all of these examples involved the use of incapacitating agents as an offensive tactical weapon as opposed to controlling crowds for defensive purposes. World War I marked the birth of RCA as chemical weapons. Both German and French forces used a wide variety of irritating agents. Bromoacetone was the most widely used lacrimator agent at that time. At the end of World War I, the US military investigated the use of chloroacetophenone (CN) as a chemical irritant and this compound was the most widely used RCA up until World War II (Olajos and Stopford, 2004). In 1928 2-chlorobenzylidene malononitrile (CS) was synthesized (Carson and Stoughton, 1928). As a more chemically stable compound and having a greater potency with less toxicity than CN, it gradually replaced CN as the preferred RCA. CS was widely used during the Vietnam War.

Many incapacitating agents were developed during the Cold War which produced either limited lethality and/or prolonged morbidity. Consequently, incapacitating agents have been banned by international treaties recognized by the USA, including CWC. Specifically, the CWC has placed a ban on the development, production, and possession of any chemical weapon intended to cause death or "temporary incapacitation". The USA considers these broad incapacitating agents as chemical warfare agents. However, the USA does not recognize these compounds as CWAs, and therefore, US policy considers them to be legal for use by civilian police or the military. The CWC does prohibit their use in times of war. Thus, the USA has opted not to utilize RCA in Iraq during the early 21st century against organized and armed insurgents.

Oleoresin capsicum (OC) spray, an extracted resin from *Capsicum* pepper plants, was first developed in the 1970s as an alternative to CS and CN agents (Spicer and Almirall, 2005). Commercially available OC sprays used by the public are approximately 1% capsaicin, while formulations used by law enforcement agencies can contain up to 15% capsaicin. Most recently, a synthetic form of capsaicin, PAVA, gained popularity as a defensive aerosol in the early 1990s (Olajos and Stopford, 2004).

PAVA Spray

While many areas do not regulate the sale or use of pepper spray, some countries and states prohibit its usage against humans, others allow people at least eighteen years of age, and others permit it solely for usage against dangerous animals.

PAVA is commercially available in two forms, Captor I and Captor II. Captor I contains 0.3% PAVA with a solvent of equal parts ethanol and water. Captor II contains 0.3% PAVA with propylene glycol, water, and ethanol (Hilmas et al., 2009).

PAVA spray is dispensed from a hand-held canister in a liquid stream. The propellant is nitrogen. PAVA is significantly more potent than CS. The liquid stream is a spray pattern and has a maximum effective range of up to 4 metres. Maximum accuracy, however, will be achieved over a distance of 1.25 - 2 metres. PAVA primarily affects the eyes causing closure and severe pain.

In order for PAVA to be effective, it must get into the eyes. The pain to the eyes is reported to be higher

than that caused by CS (Smith et al., 2004). The effects are immediate but will subside 15–20 min after exposure to fresh air. The effectiveness of PAVA is not guaranteed, however, against those under the influence of alcohol and the Smith et al. (2004) study mentions a number of cases where PAVA was used without effect.
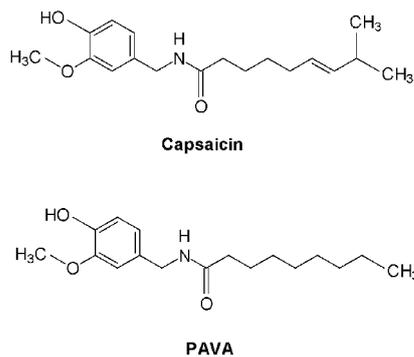
Figure 1. Chemical structures of capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) and PAVA (Pelargonic Acid Vanillylamide, N-[(4-hydroxy-3-methoxyphenyl)methyl] nonanamide).

PAVA Chemistry

Pelargonic acid vanillylamide (PAVA or nonivamide), chemically N-[(4-hydroxy-3-methoxyphenyl)methyl]nonanamide, CAS Registry Number 2444-46-4, is solid compound with melting point of 54 °C. PAVA is near analog of capsaicin (Fig. 1). PAVA as well as other synthetic compounds derived from capsaicin are known as capsaicinoids. PAVA was originally found to be a minor component in *Capsicum annum* peppers (Constant and Cordell, 1996). The majority of PAVA used in sprays is derived from synthesis rather than extraction from natural plant sources. PAVA was first synthesized by Nelson (1919). As a result, the composition and concentration of PAVA can remain consistent (Haber et al., 2007).

MECHANISM OF BIOLOGICAL ACTION

PAVA, analogous to other capsaicinoids, interacts with a population of neuropeptide containing afferent neurons and activates a vanilloid receptors (Szallasi and Blumberg, 1990, 1999). There seems to be a requirement by the receptor for a vanilloid ring and an acyl chain moiety for activity (Caterina and Julius, 2001). Vanilloid receptors are part of a superfamily of transient receptor potential (TRP) non-selective ion channels (Montell et al., 2002) with a wide variety of conductances in protein-free lipid bilayers form from a mixture of zwitterionic phospholipids (Feigin et al., 1995).

Binding of a vanilloid-containing ligand to the receptor causes channel opening, influx of Ca^{2+} and Na^+, depolarization of the neuron, and release of neuropeptides (Martling, 1987). Activation of these receptors leads to a prolonged refractory period, indicative of an apparent nonconducting, desensitized state of the receptor. In this refractory period, primary afferents become unresponsive to further application of capsaicinoids. Furthermore, it has been suggested that influx of Ca^{2+} and Na^+ may lead to rapid cellular damage and eventual cell death (Jancso et al., 1984), possibly by Ca^{2+}-dependent protease activity. Administration of capsaicin in neonatal rats causes destruction of the dorsal root ganglion neurons (Jancso et al., 1977).

The biological actions of capsacinoids are primarily due to release of the neuropeptide called substance P, calcitonin generelated peptide (CGRP), and neurokinin A from sensory neurons. These transmitters from primary sensory neurons communicate with other cell types. They produce alterations in the airway mucosa and neurogenic inflammation of the respiratory epithelium, airway blood vessels, glands, and smooth muscle (Wang, 2005). It leads to bronchoconstriction, increased vascular permeability, edema of the tracheobronchial mucosa, elevated mucosal secretion, and neutrophil chemotaxis (Lundberg and Saria,

1982; Lundberg et al., 1983, 1984). In addition, substance P can cause bronchoconstriction through stimulation of c-fibers in pulmonary and bronchial circulation (Reynolds et al., 1997) and plays a significant role in the release of mast cell renin in ischemia/reperfusion and in the activation of a local cardiac RAS. This culminates in angiotensin production, norepinephrine release, and arrhythmic cardiac dysfunction (Morrey et al., 2010).

TOXICITY

RCA produce a wide variety of physiological effects in man and PAVA is not an exception. The predominant clinical effects manifest namely in eye, lung, and skin. RCA also cause nasal, oral, neuronal, and gastrointestinal effects.

Ophtalmotoxicity

Capsacinoids cause conjunctivitis, periorbital edema/erythema, ophthalmodynia, blepharospasm, blepharitis, corneal abrasions, and lacrimation (Epstein and Majmudar, 2001; Holopainen et al., 2003; Kniestedt et al., 2005). In mice, a single subcutaneous injection of 12.5, 25, or 50 mg/kg capsaicin causes corneal changes characterized by neuronal axon degeneration in the corneal epithelium (Fujita et al., 1984). In human, there are known some retrospective studies by Watson et al. (1996) or Zollman et al. (2000). There are presented patients who transported to the emergency department following aerosol exposure from law enforcement use of OC: 56 % of individuals developed ophthalmodynia, 44 % conjunctivitis, 40 % conjunctival erythema, 13 % lacrimation, and 9 % corneal abrasions (Brown et al., 2000). All subjects reported significant eye pain, blurred vision, and lacrimation 10 min after exposure to OC pepper spray, but symptoms improved within 1 h. Corneal abrasions were not apparent, but 21% of subjects showed evidence of punctuate epithelial erosions and reduced corneal sensitivity. Corneal abnormalities were absent 1 week later.

Capsaicin directly applied to the eye causes a neurogenic inflammation, involving vasodilatation and extravasation of fluid, and unresponsiveness to chemical stimuli (Hilmas et al., 2009). Das et al. (2005) report a case of moderate-grade chemical injury to an eye following exposure to capsicum spray. A 75-year-old man presented with chemical injury to the conjunctiva and cornea following exposure to capsicum spray. The corneal epithelial defect healed in 2 weeks following the initiation of medical treatment. His unaided visual acuity had improved to 6/18 (6/9 with pinhole) after 6 weeks.

Respiratory Toxicity

Nationwide there have been numerous reports of pepper spray-related injuries, including officers injured in pepper spray-related training exercises (Miller and Skolnick, 2006). Winograd (1977) and Billmire and his co-workers (1996) show that capsaicin spray in children, has caused a severe bronchospasm and pulmonary edema (Winograd, 1977; Billmire et al., 1996). In the Billmire study (1996), a 4-week old infant was exposed to 5% pepper spray after discharge from a selfdefense device. The infant suffered respiratory failure and hypoxemia, requiring immediate extracorporeal membrane oxygenation. Inhaled capsaicin causes an immediate increase in airway resistance and caused bronchoconstriction is dose dependent (Fuller, 1991). Although generally assumed to be safe and effective, the consequences of OC cannot be predicted with certainty (Chan et al., 2002). Capsaicin nasal challenge produced symptoms of burning, congestion, and rhinorrhea (Sanico et al., 1997).

Cardiovascular Toxicity

RCA have been shown to have a direct effect on the heart (Worthington and Nee, 1999) but there are no relevant study about capsacinoids (Hilmas et al., 2009).

Gastrointestinal Toxicity

There are no studies of PAVA gastrointestinal toxicity but capsaicin causes effects on gastric mucosa including mild erythema, edema, epithelial cell damage (Desai et al., 1976), and gastric hemorrhage (Viranuvatti et al., 1972; Desai et al., 1977; Kumar et al., 1984). Nausea has also been reported in individuals exposed to spice powder containing capsaicin (Hay et al., 2006).

Dermatological Toxicity

Capsaicinoids may have a vesicant effect, depending on length of exposure, in most cases it produces a burning sensation and mild erythema. Capsaicins cause erythema and burning pain without vesiculation when applied topically to human skin (Burnett, 1989; Watson et al., 1996).

Neurotoxicity

Capsacinoids activate receptors in trigeminal and intestinal neurons. These include pain receptors located in the mouth, nose, stomach, and mucous membranes (Lee et al., 1991). Trigeminal neurons utilize substance P as their primary pain neurotransmitter. Capsaicin first induces the release of substance P from the neuron and then blocks the synthesis and transport of substance P to the effector side (Bernstein et al., 1981). Substance P depolarizes neurons to produce stimulation of smooth muscle, dilation of blood vessels, and activation of sensory nerve endings (Tominack and Spyker, 1987). Substance P is also associated with sensory or skin inflammation afferents. This peptide is also a peripheral mediator of neurogenic inflammation and smooth muscle contraction (Lembeck and Holzer, 1979).

HUMAN LETHALITY

Capsaicinoids, found in less-than-lethal self-defense weapons, have been associated with respiratory failure and death in exposed animals and people (Reilly et al., 2003). Human deaths have been reported from RCA exposure (Thorburn, 1982; Danto, 1987). Death is usually the result of excessive concentrations used, confined spaces, and prolonged exposures in spite of OC are allowed to be safe substance with low toxicity (Clede, 1993). More research should be conducted in light of recent deaths involving pepper spray use by law enforcement agencies. One case involving an inmate who died in custody implicated pepper spray as a direct contributor to death (Steffe et al., 1995). Billmire et al. (1996) reported the life-threatening effects in a 4-week old infant exposed to OC spray as a result of an accidental discharge. Polish authors (Niemcunowicz-Janica et al., 2009) described rare case of a sudden death of a young man, caused by an oleoresin capsicum spray. In consequence, the victim developed acute laryngeal edema and death by asphyxiation.

RISK ASSESSMENT

When used as intended, RCA are thought to be safe and of sufficient low toxicity. They are designed with the purpose of disabling a targeted individual through sensory irritation of the eyes, respiratory tract, and skin. They are not without additional, unwanted effects especially in circumstances where high concentrations are used or exposure is prolonged (Patterson et al., 2004). The modern RCA used today include PAVA have low risk assessment (Busker and van Helden, 1998).

PEPPER SPRAY TREATMENT

No effective treatment exists to counter the effect of pepper spray (Barry et al., 2008). An individual may try to relieve symptoms by blinking continuously and thereby producing tears to flush out the chemicals. However, as the effect of the chemicals causes the eyes to shut, blinking becomes excessively difficult. Flushing affected areas with a mild soap and using a fan may bring limited relief. Water is ineffective as capsaicin and PAVA are not soluble in water.

CONCLUSIONS

Capsaicinoids gained considerable attention in the 1990s from police departments and the public at large for safe, effective chemical incapacitation of individuals. These compounds are primarily used as defensive sprays by law enforcement to subdue a combative suspect or by individuals for selfprotection.

However, there are several cases which illustrate that the safety of the commercially available pepper sprays should be assessed before marketing as they may cause serious injury, for example to the eyes. Despite these dangers many people find pepper spray as legitimate means of self-defense.

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REFERENCES

1. Barry, J.D., Hennessy, R., McManus, J.G. Jr. A randomized controlled trial comparing treatment regimens for acute pain for topical oleoresin capsaicin (pepper spray) exposure in adult volunteers. *Prehosp. Emerg. Care.* **2008**, 12, 432-437.
2. Bernstein, J.E., Swift, R.M., Soltani, K. Inhibition of axon reflex vasodilation by topically applied capsaicin. *J. Invest. Dermatol.* **1981**, 76, 394–395.
3. Beswick, F.W. Chemical agents used in riot control and warfare. *Hum. Exp. Toxicol.* **1983**, 2, 247-256.
4. Billmire, D., Vinocur, C., Ginda, M. Pepper spray induced respiratory failure treated with extracorporeal membrane oxygenation. *Pediatrics* 1**996**, 98, 961–963.
5. Brown, L., Takeuchi, D., Challoner, K. Corneal abrasions associated with pepper spray exposure. *Am. J. Emerg. Med.* **2000**, 18, 271-272.
6. Burnett, J.W. Capsicum pepper dermatitis. *Cutis* **1989**, 43, 534.
7. Busker, R.W., van Helden, H.P.M. Toxicological evaluation of pepper spray as a possible pweapon for the Dutch Police force:

Risk Assessmemnt and Efficacy. *Am. J. Forensic Med. Pathol.* **1998**, 19, 309-316.

8. Carson, B.B., Stoughton, R.W. Reactions of alpha, beta-unsaturated dinitriles. *J. Am. Chem. Soc.* **1928**, 50, 2825.

9. Caterina, M.J., Julius, D. The vanilloid receptor: a molecular gateway to the pain pathway. *Ann. Rev. Neurosci.* **2001**, 24, 487–517.

10. Chan, T.C., Vilke, G.M., Clausen, J., Clark, R.F., Schmidt, P., Snowden, T., Neuman, T. The effect of oleoresin capsicum "pepper" spray inhalation on respiratory function. *J. Forensic Sci.* **2002**, 47, 299-304.

11. Clede, B. Oleoresin capsicum. Law Order 1993 (March): 63. Constant, H.L., Cordell, G.A., West, D.P. Nonivamide, a constituent of capsicum oleoresin. *J. Nat. Prod.* **1996**, 59: 425–426.

12. Danto, B. Medical problems and criteria regarding the use of tear gas by police. *Am. J. Forensic Med. Pathol.* **1987**, 8, 317–322.

13. Das, S., Chohan, A., Snibson, G.R., Taylor, H.R. Capsicum spray injury of the eye. *Int. Ophtalmol.* **2005**, 26, 171-173.

14. Desai, H.G., Venugopalan, K., Antia, F.P. The effect of capsaicin on the DNA content of gastric aspirate. *Indian J. Med. Res.* **1976**, 64, 163–716.

15. Desai, H.G., Venugopalan, K., Philipose, M. Effect of red chili powder on gastric mucosal barrier and acid secretion. *Indian J. Med. Res.* **1977**, 66, 440–448.

16. Epstein, R.J., Majmudar, P.A. Pepper spray in the eye. *Ophthalmology.* **2001**, 108, 1712-1713.

17. Feigin, A.M., Aronov, E.V., Bryant, B.P., Teeter, J.H., Brand, J.G. Capsaicin and its analogs induce ion channels in planar lipid bilayers. *Neuroreport.* **1995**, 6, 2134-2136.

18. Fujita, S., Shimizu, T., Izumi, K., Fukada, T., Sameshima, M., Ohba, N. Capsaicin-induced neuroparalytic keratitislike corneal changes in the mouse. *Exp. Eye Res.* **1984**, 38, 165–175.

19. Fuller, R.W. Pharmacology of inhaled capsaicin. *Respir. Med.* **1991**, 85, Supp. A, 31–34.

20. Haber, L., Nance, P., Maier, A., Price, P., Olajos, E., Bickford, L., McConnell, M., Klauenberg, B.J. Human effectiveness and risk characterization of oleoresin capsicum (OC) and pelargonic acid vanillylamide (PAVA or nonivamide) handheld devices. Air Force Research Laboratory, *DTIC Technical Report No. ADA476262*, **2007**, 254 p.

21. Hay, A., Giacaman, R., Sansur, R., Rose, S. Skin injuries caused by new riot control agent used against civilians on the West Bank. *Med. Confl. Surviv.* ,**2006**, 22, 283–291.

22. Hilmas, C.J., Poole, M.J., Katos, A.M., Williams, P.T. Riot control agents. In: Gupta, R.C. (Ed.). Handbook of Toxicology of Chemical Warfare Agents. *Elsevier*, **2009**, pp. 153-175. ISBN: 978-0-12-374484-5

23. Holopainen, J.M., Moilanen, J.A., Hack, T., Tervo, T.M. Toxic carriers in pepper sprays may cause corneal erosion. *Toxicol Appl Pharmacol.* **2003**, 186, 155-162.

24. Horká, J. History of Chemical Wars (Article in Czech). *Thesis*, **2007**, 91 p. Faculty of Health and Social Studies, University of South Bohemia České Budějovice, Czech Republic.

25. Huntington, M.K., Gavagan, T.F. Disaster medicine training in family medicine: A review of the evidence. *Farm. Med.* **2011**, 43, 13-20.

26. Jancso, G., Karcsu, S., Kiraly, E., Szebeni, A., Toth, L., Bacsy, E., Joo, F., Parducz, A. Neurotoxin-induced nerve cell degeneration: possible involvement of calcium. *Brain Res.* **1984**, 295, 211–216.

27. Jancso, G., Kiraly, E., Jancso-Gabor, A. Pharmacologically induced selective degeneration of chemosensitive primary sensory neurons. *Nature* **1977**, 270, 741–743.

28. Kniestedt, C., Fleischhauer, J., Stürmer, J., Thiel, M.A. Pepper spray injuries of the anterior segment of the eye. [Article in German] *Klin. Monb. Augenheilkd.* **2005**; 222, 267-270.

29. Kumar, N., Vij, J.C., Sarin, S.K. Do chillis influence healing of duodenal ulcer *Br. Med. J.* **1984**, 288, 1883.

30. Lee, S.S., Sohn, Y.W., Yoo, E.S., Kim, K.H. Neurotoxicity and long lasting analgesia induced by capsaicinoids. *J. Toxicol. Sci.* **1991**, 16, Suppl 1, 3-20.

31. Lembeck, F., Holzer, P. Substance P as neurogenic mediator of antidromic vasodilation and neurogenic plasma extravasation. Naunyn-Schmied. *Arch. Pharmacol.* **1979**, 319, 175–193.

32. Lumb, R.C., Friday, P.C. Impact of pepper spray availability on police officer use-of-force decisions. *Int. J. Police Strat. Manag.* **1997**, 20, 136 – 148.

33. Lundberg, J.M., Brodin, V., Hua, X., Saria, A. Vascular permeability changes and smooth muscle contraction in relation to capsaicin-sensitive substance P afferents in the guinea

pig. *Acta Physiol. Scand.* **1984**, 120, 217–227.

34. Lundberg, J.M., Brodin, E., Saria, A. Effects and distribution of vagal capsaicin-sensitive substance P neurons with special reference to the trachea and lungs. *Acta Physiol. Scand.* **1983**, 119, 243–252.

35. Lundberg, J.M., Saria, A. Bronchial smooth muscle contraction induced by stimulation of capsaicin-sensitive sensory neurons. *Acta Physiol. Scand.* **1982**, 116, 473–476.

36. Martling, C.R. Sensory nerves containing tachykinins and CGRP in the lower airways. *Acta Physiol. Scand.* **1987**, 130, Suppl. 563, 1–57.

37. Miller, J.J., Skolnick, J. Inhalation injury after capsaicin exposure. *J. Ky. Med. Assoc.* **2006**, 104, 103-105.

38. Montell, C., Birnbaumer, L., Flockerzi, V., Bindels, R.J., Bruford, E.A., Caterina, M.J., Clapham, D.E., Harteneck, C., Heller, S., Julius, D., Kojima, I., Mori, Y., Penner, R., Prawitt, D., Scharenberg, A.M., Schultz, G., Shimizu, N., Zhu, M.X. A unified nomenclature for the superfamily of TRP cation channels. *Molecular Cell.* **2002**, 9, 229–241.

39. Morrey, C., Brazin, J., Seyedi, N., Cort,i F., Silver, R.B., Levi, R. Interaction between sensory C-fibers and cardiac mast cells in ischemia/reperfusion: activation of a local renin-angiotensin system culminating in severe arrhythmic dysfunction. *J Pharmacol Exp Ther.* **2010**, 335, 76-84.

40. Nelson, E.K. Vanillyl-acyl amides. *J. Am. Chem. Soc.* **1919**, 41, 2121–2130.

41. Niemcunowicz-Janica, A., Ptaszynska-Sarosie, I., Wardaszka, Z. Sudden death caused by an oleoresin capsicum spray. [Article in Polish]. *Arch. Med. Sadowej Kryminol.* **2009**, 50, 252-254.

42. Olajos, E., Stopford, W. (Eds.). Riot Control Agents. *Informa Healthcare, New York* **2004**, p. 1–15.

43. Olajos, E.J., Salem, H. Riot control agents: Pharmacology, toxicology, Biochemistry and chemistry. *J. Appl. Toxicol.* **2001**, 21, 355-391.

44. Patterson, J., Hakkinen, B., Nance, P., Dourson, M., Klauenberg, B.J. An approach for assessing and characterizing risk from the use of riot control agents. In: (Olajos, E., Stopford, W., Eds), Riot Control Agents, **2004**, pp. 1–15. *Informa Healthcare, New York*.

45. Reilly, C.A., Taylor, J.L., Lanza, D.L., Carr, B.A., Crouch, D.J., Yost, G.S. Capsaicinoids cause inflammation and epithelial cell death through activation of vanilloid receptors. *Toxicol. Sci.* **2003**, 73, 170-181.

46. Reynolds, P.N., Holmes, M.D., Scicchitano, R. Role of tachykinins in bronchial hyper-responsiveness. *Clin. Exp. Pharmacol. Physiol.* **1997**, 24, 273-280.

47. Robinson, J.P. (Ed.). The problem of chemical and biological warfare, Vol. 1. In The Rise of CB Weapons: A Study of the Historical, Technical, Military, Legal and Political Aspects of CBW, and Possible Disarmament Measures. *Humanities Press*, **1971**, p. 110–156.

48. Sanico, A.M., Atsuta, S., Proud, D., Togias, A. Dose-dependent effects of capsaicin nasal challenge: in vivo evidence of human airway neurogenic inflammation. *J. Allergy Clin. Immunol.* **1997**, 100, 632-641.

49. Smith, C.G., Stopford, W. Health hazards of pepper spray. *N C Med J.* **1999**, 60, 268-274.

50. Smith, G., MacFarlane, M., Crockett, J. Comparison of CS and PAVA: Operational and Toxicological Aspects. *Home Office Police Scientific Development Branch, UK,* **2004**. Publication Number 88/04.

51. Spicer, O. Jr, Almirall, J.R. Extraction of capsaicins in aerosol defense sprays from fabrics. *Talanta.* **2005**, 67, 377-382.

52. Steffe, C.H., Lantz, P.E., Flannagan, L.M., Thompson, R.L., Jason, D.R. Oleoresin capsicum (pepper) spray and "in-custody deaths". *Am. J. Forens. Med. Pathol.* **1995**, 16, 185–192.

53. Szallasi, A., Blumberg, P.M. Vanilloid receptor loss in rat sensory ganglia associated with long term desensitization to resiniferatoxin. *Neurosci. Lett.* **1992**, 140, 51–54.

54. Szallasi, A., Blumberg, P.M. Vanilloid (capsaicin) receptors and mechanisms. *Pharmacol. Rev.* **1999**, 51, 159–212.

55. Thorburn, K.M. Injuries after use of the lacrimatory agent chloroacetophenone in a confined space. *Arch. Environ. Health* **1982**, 37, 182–186.

56. Tominack, R.L., Spyker, D.A. Capsicum and capsaicin – a review: case report of the use of hot peppers in child abuse. *Clin. Toxicol.* **1987**, 25, 591–601.

57. Viranuvatti, V., Kalayasiri, C., Chearani, O. Effects of capsicum solution on human gastric mucosa as observed gastroscopically. *Am. J. Gastroenterol.* **1972**, 58, 225–232.

58. Wang, D.H. The vanilloid receptor and hypertension. *Acta Pharmacol Sin.* **2005**, 26, 286-294.

59. Watson, W.A., Stremel, K.R., Westdorp, E.J. Oleoresin capsicum (cap-stun) toxicity from aerosol exposure. *Ann. Pharmacother.* **1996**, 30, 733–735.

60. Winograd, H.L. Acute croup in an older child. An unusual toxic origin. *Clin. Pediatr. (Phila.)* **1977**, 16, 884–887.

61. Worthington, E., Nee, P. CS exposure – clinical effects and management. *J. Accid. Emerg. Med.* **1999**, 16, 168–70.

62. Zollman, T.M., Bragg, R.M., Harrison, D.A. Clinical effects of oleoresin capsicum (pepper spray) on the human cornea and conjunctiva. *Ophthalmology* **2000**, 107, 2186–2189.