World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

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Acetaminophen: Ancient drug with a novel analgesic mechanism of action

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World Journal of Advanced Research and Reviews, 2022, 16(01), 580–589

Publication history: Received on 11 September 2022, revised on 13 October 2022, accepted on 16 October 2022

Article DOI: https://doi.org/10.30574/wjarr.2022.16.1.1046

Abstract

Paracetamol is used worldwide for its analgesic and antipyretic actions. Its spectrum of activity similar to that of NSAIDs and resembles particularly the COX-2 selective inhibitors,but with a lesser anti-inflammatory effect, its metabolism is complex, and its analgesic mechanisms have not been completely understood. It was previously explained to produce analgesia by inhibiting the enzyme cyclooxygenase (COX) which is incorrect, however recent findings revealed that acetaminophen is metabolized to p-aminophenol, which crosses the blood-brain barrier and get metabolized by fatty acid amide hydrolase (FAAH) to yield N-acylphenolamine (AM404). AM404 acts on a number of receptors viz; the transient receptor potential vanilloid-1 (TRPV1) and cannabinoid 1 (CB1) receptors in the midbrain and medulla which are mediators of pain modulation. Moreover it has also been reported to act via Cav3.2 calcium channel. Evidence also show that acetaminophen analgesic action of acetaminophen could be due to its interaction with endogenous neurotransmitter systems, opioid, serotonergic systems and nitric oxide system. additionally, it is also been unraveled that paracetamol may exert novel mechanisms of action, likely relevant for their analgesic action, by modulating protein kinase C epsilon (PKCε) and substance P (SP) in the peripheral sensory neurons. This review is geared towards explaining and updating with experimental proof the analgesic novel mechanism of action of Acetaminophen since it has no ant-inflammory effect

Keywords: N-acylphenolamine (AM404); PKCε; Acetaminophen; Analgesia; Cyclooxygenase

1. Introduction

Acetaminophen is one of the most commonly used analgesic agents for alleviating acute and chronic pain. Due to its safety, acetaminophen is prescribed for patients in whom non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated, such as those with gastric ulcers and bronchial asthma, pregnant women, nursing mothers, and children [1]. It has also been placed on all three steps of pain treatment intensity of the WHO analgesic ladder for the treatment of cancer pain. However, its metabolism is complex, and its analgesic mechanisms have not been completely understood. Previously, it was believed that acetaminophen produced analgesia by inhibiting the enzyme cyclooxygenase (COX), however recent research revealed that acetaminophen is metabolized to p-aminophenol, which crosses the blood-brain barrier and gets metabolized by fatty acid amide hydrolase (FAAH) to yield N-acylphenolamine (AM404). AM404 acts on a number of receptors viz; the transient receptor potential vanilloid-1 (TRPV1) and cannabinoid 1 (CB1) receptors in the midbrain and medulla [2] which are co-localized mediators of pain modulation [3]. It has also been reported to act via Cav3.2 calcium channel [4]. Another possible reason for the analgesic action of

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acetaminophen could be its interaction with endogenous neurotransmitter systems,opioid, serotonergic systems and nitric oxide system [5,6]. It is also been unraveled that paracetamol may exert novel mechanisms of action, likely relevant for their analgesic action, by modulating protein kinase C epsilon (PKCε) and substance P (SP) in the peripheral sensory neurons [7]. Therefore, acetaminophen produce analgesia via direct action on the brain, and these receptor sites on the brain are the main mediators of acetaminophen-induced analgesia. Moreover, recent study revealed a new analgesic mechanism of acetaminophen, using behavioral measures, in vivo and in vitro whole-cell patch-clamp recordings with rats, wherein the acetaminophen metabolite. AM404 directly induces analgesia via TRPV1 receptors on the spinal dorsal horn in a rat model of inflammatory pain, and these analgesic effects were stronger in the inflammatory pain model than in naïve rats [8]. Similar to the brain, the spinal cord, especially substantia gelatinosa (SG, lamina II of Rexed), is also critical to pain pathways, and modulates nociceptive transmission via primary afferent Aδ- and C-fibers. Furthermore, TRPV1 receptors are abundant in the spinal cord dorsal horn [9]. Therefore, results describes the new analgesic mechanism underlying the action of acetaminophen on the spinal dorsal horn, are consistent when compared to previous reports [8]. Paracetamol is largely used as an analgesic and antipyretic, which, because of its lesser anti-inflammatory activity and poorer inhibition of COX_1 and $COX\text{-}_2$,[10,11] has not traditionally been considered a NSAID. Therefore, even though it has always been discussed together with NSAIDs in terms of pharmacological mechanism, acetaminophen is not regarded as an NSAID and is not indicated for treating inflammatory pain conditions.

The purpose of this review is to summarize the primordial and novel issues related to the analgesic mechanisms of action of acetaminophen. This review will allow health caregivers especially clinicians to consider new pain management modality using acetaminophen, and tutors of pharmacology would also find the review a useful one.

2. Primordial analgesic mechanisms of action of acetaminophen

2.1. Inhibition of Cyclooxygenase enzyme Activity

In his Nobel Prize-winning work on the mechanism of action of aspirin and other NSAIDs, [12] demonstrated that these drugs inhibit the formation of prostaglandins (PGs), local factors that are associated with pain, fever and inflammation. However, paracetamol did not appear to inhibit PG synthesis, despite its actions similar to those of the NSAIDs. The mechanism of the basic pharmacological effects of paracetamol is only now becoming clear and it is now recognized to be an inhibitor of PG synthesis in cellular systems under specific conditions and has an apparent selectivity for one of the cyclooxygenase (COX) enzymes, namely COX-2. Previously, evidence were provided that the hypothermic action of paracetamol in normothermic mice is dependent on inhibition of a COX-1 gene-derived protein [13]. This conclusion was derive from the demonstration that the brain PGE2-dependent paracetamol-induced hypothermia was significantly attenuated in COX-1-/- mice, and was completely retained in COX-2-/- , in comparison to the respective littermate wild-type controls. The two likely targets for the paracetamol-induced hypothermia are either COX-1 or its variant COX-3.

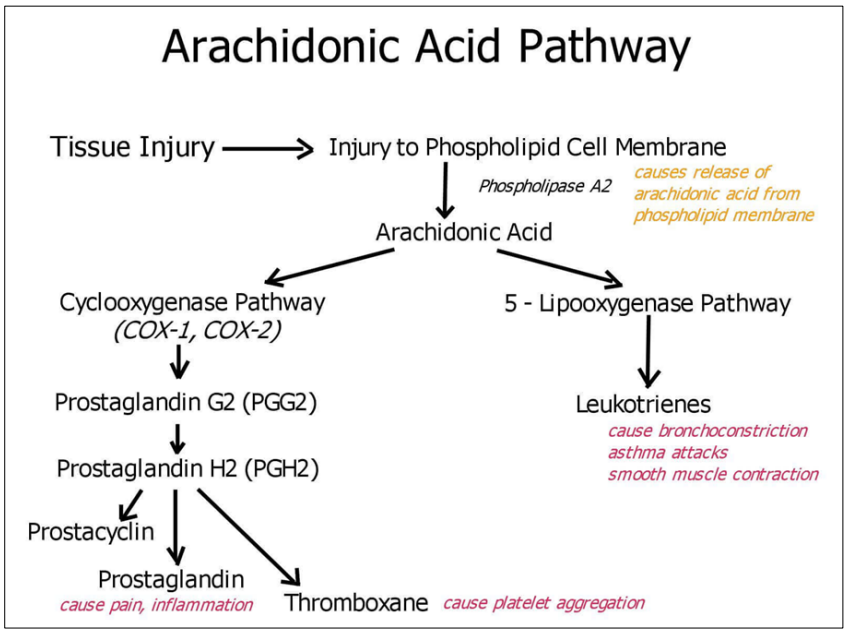

Figure 1 prostaglandin synthesis from arachidonic acid

The dual actions of cyclooxygenase-1 (COX-1) and COX-2 are important considerations in any discussion of the effects of paracetamol and related drugs. Both COX- 1 and COX-2 catalyze the production of PGG_2 from the most common substrate, arachidonic acid, which is liberated from phospholipid by the activity of cPLA2-®. This reaction is catalyzed by the cyclooxygenase activity of the enzymes. The peroxidase function of the enzymes then converts PGG_2 to PGH_2 which is the branch point for the formation of the various prostanoids such as PGE_2, prostacyclin and thromboxane A_2. Thus, specific enzymes catalyse the formation of these various prostanoids from the common intermediate, PGH_2. $COX\text{-}_1$ and $COX\text{-}_2$ are very similar in structure. Their peroxidase functions and active sites are closely related to that of myeloperoxidase, the neutrophil enzyme which catalyzes the formation of hypochlorous acid [14]. Both COX-1 and myeloperoxidase metabolize paracetamol to reactive oxidized species and it is likely that COX-2 oxidises paracetamol [15]. The synthesis of PGs appears to be compartmentalised [16]. According to this scheme, low concentrations of arachidonic acid, either available extracellularly or released from phospholipid by cPLA2-®, are largely converted to PGH_2 by COX-2 when both isoenzymes are present in the cell. The intermediate, PGH_2, is then converted to PGE_2 by membrane associated PGE synthase [16]. This is called the delayed response because this pathway requires induction by cytokines in inflammatory cells although it is likely to be constitutive in cells of the central nervous system. By contrast, the immediate system utilises COX-1 and cytosolic PGE synthase when high concentrations of arachidonic acid are available, either through high concentrations of exogenous material or by "explosive" activation of cytosolic phospholipase A2-® (cPLA2-®) by calcium ionophore [16].This scheme has been developed from macrophages and its general validity remains to be established. Paracetamol is a weak inhibitor of PG synthesis in tissue homogenates or on purified COX-1 or COX-2. Yet, the effects of paracetamol are in vivo generally consistent with inhibition of PG synthesis and, in particular, with selective inhibition of COX-2.

However, [17] reported that it appeared that COX-3 is not found in humans, and further studies suggest that acetaminophen has no clinically significant effects on the COX-1 exon splice variants found in humans so far. It is now considered that the inhibition of COX activity is not the main analgesic mechanism of acetaminophen hence this review.

3. Novel analgesic mechanism of action of acetaminophen

3.1. Activating the Transient Receptor Potential Vanilloid 1 and Cannabinoid 1 Receptors

Acetaminophen is first metabolized to p-aminophenol, which easily crosses the blood-brain barrier and is converted to AM404 by fatty acid amide hydrolase [18]. Acetaminophen is also metabolized to other compounds through another pathway, such as N-acetyl-p-benzoquinoneimine (NAPQI), which is also reported to exert analgesic effect by activating transient receptor potential ankyrin 1 receptors and on CB1 receptors [19,20]. However, AM404 is widely known to be the most important mediator of acetaminophen metabolite-induced analgesia. In particular, it is known that TRPV1 receptors in the brain are important for pain modulation. Two examples involving TRPV1 receptors are cannabidiol, the primary non addictive component of cannabis, which induces analgesia through TRPV1 receptor activation in the dorsal raphe nucleus [21] and dipyrone, an antipyretic and non-opioid analgesic drug which causes analgesia by acting on TRPV1 and CB1 receptors in rostral ventromedial medulla [22]. Therefore, it is now considered that AM404 acts on TRPV1 receptor in the brain and induces analgesia. For example, [23,24] opined that by activating TRPV1 receptor, AM404 produced outward currents that were measured using whole-cell patch-clamp recordings as a model and acted as a partial agonist in trigeminal neurons. These receptors in the brain are widely considered to be the main mediators of acetaminophen-induced analgesia. Ohashi and his team recently revealed a new analgesic mechanism of acetaminophen, using behavioral measures, and in vivo and in vitro whole-cell patch-clamp recordings with naïve rats [8], him and his team demonstrated with behavioral experiments that intraperitoneal injections of acetaminophen and intrathecal injections of AM404 induce analgesia to thermal stimulation. The team subsequently conducted in vivo and in vitro whole-cell patch-clamp recordings of SG neurons in the spinal cord dorsal horn and recorded the excitatory post-synaptic currents (EPSCs). With in vivo patch-clamp recording, the areas under the curve, which is surrounded by the baseline and border of the EPSCs, were significantly reduced after intravenous injection of acetaminophen following peripheral pinch stimuli. However, with in vitro patch clamp recording, direct application of acetaminophen to the spinal cord did not change miniature EPSCs (mEPSCs), but AM404 did. These results suggest that systemic administration of acetaminophen metabolizes to AM404,

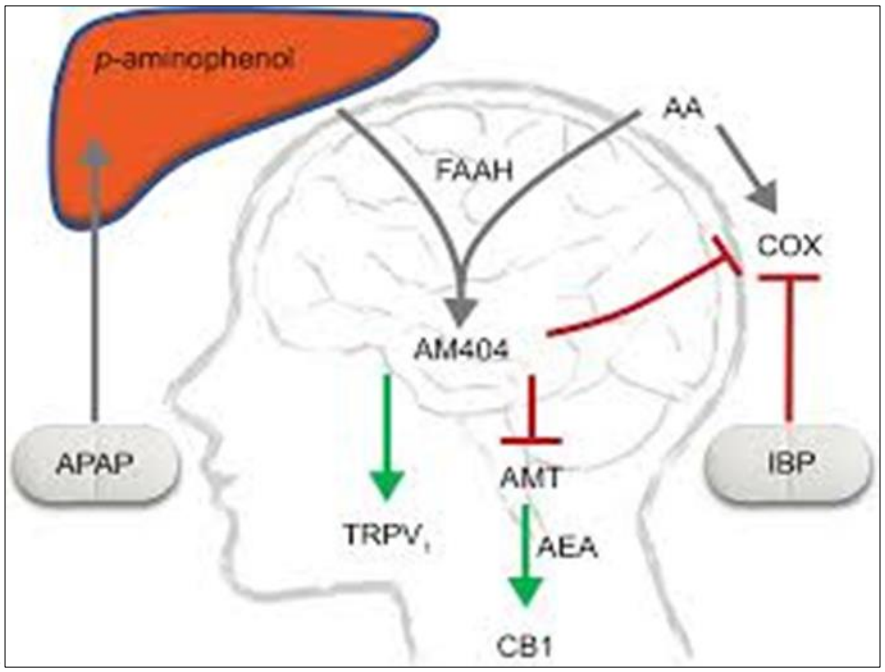

Figure 2 Metabolism of acetaminophen

Simplified peripheral schematic diagram of arachidonic acid metabolism, APAP undergoes deacetylation in the liver. The metabolite *p*-aminophenol enters the central nervous system where it is conjugated to arachidonic acid by FAAH to produce AM404. AM404 activates $TRPV_1$ and cannabinoid receptors. AM404 also inhibits anandamide membrane transporters, leading to an increase in the endogenous cannabinoid receptor agonist anandamide. Both IBP and AM404 inhibit COX enzyme binding to arachidonic acid and downstream prostaglandin synthesis. These mechanisms of action are believed to produce the analgesic action of APAP.

Abbreviations

AA: Arachidonic acid,
AEA: Anandamide,AM404, N-(4-Hydroxyphenyl) arachidonylamide,
AMT: Anandamide membrane transporters,
APAP: Acetaminophen,
CB1: Cannabinoid receptor type 1,
COX: Cyclooxygenase,
FAAH: Fatty acid amide hydrolase,
IBP: Ibuprofen,
$TRPV_1$: Transient receptor potential vanilloid type 1

Which directly acts on spinal cord dorsal horn and induces analgesia. [8] also examined the effects of AM404 on EPSCs evoked from primary afferent neurons by stimulating the dorsal root and demonstrated that AM404 reduces the amplitudes of monosynaptic EPSCs evoked by stimulating C-fibers, but not Aδ-fibers. These responses were inhibited by the TRPV1 receptor antagonist, but not CB1 receptor antagonist. Therefore, they found that acetaminophen was metabolized to AM404, which induces analgesia by directly inhibiting the excitatory synaptic transmission via TRPV1 receptors expressed on terminals of C-fibers in the spinal dorsal horn. Contrary to previous studies on the brain, the study did not find the analgesic effect of acetaminophen/AM404 on the CB1 receptor on spinal dorsal horn neurons. It is believe that the main reason for the differences between the results and that of previous reports was the concentration of AM404 (20 mg/kg).Therefore, there is a possibility that the concentration of AM404 in the study was insufficient to activate CB1receptors in dorsal horn neurons and higher doses of AM404 may also act on the CB1 receptor in the spinal dorsal cord. From the findings, it was believed that new analgesic mechanism of acetaminophen will contribute to the development of new modality for clinical pain management using acetaminophen.

3.2. Calcium channel receptor Cav3.2

Arachidonic-related compounds such as anandamide and 2-arachidonylglycerol also interact with T-type calcium channels, especially the Cav3.2 subtype, an effect which mediates their analgesic property [4]. Silencing of Cav3.2 using oligonucleotide antisense [25] knockout mice, or pharmacological tools resulted in decrease of pain in several pain tests, thereby confirming the strong role of this calcium channel in pain. Because AM404 is the arachidonic related metabolite of paracetamol, the role of Cav3.2 in paracetamol action was also investigated [26]. Mice with deletion of the Cav3.2−/− gene did not show any analgesic effect after paracetamol administration. In addition, the intra cerebroventricular injection of AM404 did not induce an analgesic effect in these knockout mice. To determine whether Cav3.2 in the brain is involved in the antinociceptive effect of paracetamol, TTA-A2, was injected a Cav3.2 blocker, intracerebroventricularly before administration of paracetamol. This treatment prevented the effect of paracetamol. Spinal involvement of Cav3.2 receptors was also studied by co-administering paracetamol with an intrathecal injection of TTA-A2. In contrast to the previous results, spinal blockade of Cav3.2 did not alter the analgesic effect of paracetamol, indicating that the antinociceptive effect of paracetamol is dependent on Cav3.2 located in the brain. AM404 seems to have an indirect action because it only weakly inhibited Cav3.2 currents (IC50 = 13.7 μM) recorded in DRG neurons by a whole-cell patch clamp method**.** By comparison, in the same assay, TTA-A2 had an IC50 of 9.0 nM. But neither paracetamol nor p-aminophenol inhibited Cav3.2 currents.

3.3. Serotonergic system

Serotonergic system's implication in the action of paracetamol was first described by [27] in 1991 and [28] in 1996. They demonstrated that the analgesic effect of paracetamol was reduced after lesion of the serotonergic bulbo-spinal pathway by 5,6-dihydroxytryptamine or total depletion of the central serotonin (5-HT) synthesis by p-chlorophenylalanine. These results were confirmed by another team using 5,7-dihydroxy- tryptamine [29]. The results showed that the effect produced by paracetamol was potent as observed in tissue concentrations of 5-HT in the cortex, hypothalamus, striatum, hippocampus and brainstem [28,30]. Acetaminophen-induced serotonin increases have also been confirmed in recent studies. Intraperitoneal acetaminophen administration (400 mg/kg) induced approximately 40% and 75% increases in serotonin levels in the pons and frontal cortex, respectively. These increases in serotonin levels have been found to be related to central (hydroxytryptamine) 5-HT_2 receptor and receptor subtypes, (5-HT_1 5-HT_{1A} and 5-HT_{1B}, 5-HT_2, 5-HT_3, and 5-HT_7), as well as opioid receptors (μ1 and κ) [31].

In another study, [6] examined whether acetaminophen and AM404 induce spinal 5-HT release and the mechanism through which spinal 5-HT receptor activation exerts analgesic effects in a rat formalin test in an inflammatory pain model. Spinal 5-HT release was examined by intrathecal microdialysis in conscious and freely moving rats. Acetaminophen was administered orally, and AM404 was administered intracerebroventricularly. In rat formalin tests, oral acetaminophen and intracerebroventricular AM404 induced significant spinal 5-HT release and produced analgesic effects. The analgesic effect of oral acetaminophen was partially antagonized by intrathecal administration of WAY100135 (a 5-HT_{1A} receptor antagonist) and SB269970 (a 5-HT_7 receptor antagonist). In contrast, the analgesic effect of intracerebroventricular AM404 was completely antagonized by WAY100135, while SB269970 had no effect. The data suggested that while oral acetaminophen and intracerebroventricular AM404 activate the spinal 5-HT system, the role of the spinal 5-HT system activated by oral acetaminophen differs from that activated by intracerebroventricular AM404.

All these recent studies have confirmed the idea that systemic acetaminophen administration increases serotonin levels in the brain cortex and brain stem (pons) which thus showed that acute and chronic systemic administration of acetaminophen induces changes in central serotonergic neurotransmission. It can be concluded that, despite the involvement of 5-HT_2-serotonergic and opioid receptors in acetaminophen-induced serotonin increases in some brain regions,[31] apparently the precise mechanism of action is not yet lucid as the various result did not specifically mention the mechanism (alterations in serotonin metabolism, release, or uptake) and as such needs further clarification.

3.4. The role of nitric oxide (NO) in acetaminophen analgesia

NO is widely accepted as an important messenger molecule and neurotransmitter in the central nervous system that is involved in various physiological functions [32,5]. NO plays important roles in pain transmission, either inducing hyperalgesia or exerting antinociceptive actions [35-36].

Björkman et al.[36] in 1994 pointed out the involvement of neuronal NO systems in the analgesic action of acetaminophen. Additionally and in accordance with that study, neuronal NO synthase was found to be involved in the analgesic effect of acetaminophen when acetaminophen was used in lower doses (especially with 100mg/kg, oral) in the Randall- Selitto pain model, whereas both neuronal and inducible NO synthases were found to be involved in the

analgesic action of acetaminophen in lower doses (50 and 100 mg/ kg, oral) in a writhing test. [37] also showed that acetaminophen inhibited induced NO synthesis in spinal cord tissue. As a result, it can be concluded that NO systems are involved in acetaminophen analgesia and it is more likely that suppression of the central NO systems contributes to the central analgesic mechanisms of acetaminophen. With interest on the findings related to the interaction between acetaminophen and NO, the mechanism of action of NO- acetaminophen has been suggested to be different from that of acetaminophen itself. It has been proposed that although NO-acetaminophen and acetaminophen may share some common mechanisms like COX inhibition, the sustained release of low amounts of NO when combined with acetaminophen may add different but not clearly understood pharmacological properties. Inhibition of the wind-up phenomenon indicating a mechanism of action in the central nervous system level, more probably in the spinal cord, and reduction in the amounts of some cytokines in the peripheral tissues has been proposed[38,39]. Additional to the above plentiful data related to the promising effects of NO-acetaminophen, the antinociceptive effect of intravenously as well as intrathecally administered NO-acetaminophen has also been shown in a neuropathic pain model (partial ligation of the sciatic nerve) in rats, where acetaminophen alone was ineffective. As a result, these studies showed that NO-acetaminophen can be an effective analgesic in neuropathic painful conditions.

3.5. Opioids

Another possible mechanism for the analgesic action of acetaminophen could be the action of endogenous neurotransmitter systems including opioid and serotonergic systems. Previous studies have reported that the analgesic effect of acetaminophen involve the interaction with endogenous opioid pathways that lead to analgesic spinal-supraspinal self-synergy [40], and the analgesic effects induced by intrathecal injection or intra cerebroventricular injection of acetaminophen were attenuated by mu-,delta-, and kappa-opioid receptor antagonists [41]. Another study further opined that the acetaminophen (paracetamol)-induced spinal (intrathecal, i.t.)/supraspinal (intracerebroventricular, i.c.v.) site/site antinociceptive 'self-synergy' in mice is attenuated by the opioid receptor subtype selective antagonists beta-funaltrexamine hydrochloride (beta-FNA,mu), naltrindole (delta), and nor-binaltorphine hydrochloride (nor-BNI,kappa). These findings further reveals the fact that endogenous opioids (viz,endorphins, enkephalins, and dynorphins) and their receptors are contributory to the central analgesic action of acetaminophen.

3.6. Modulation of protein kinase C epsilon (PKCε) and substance P (SP) in the peripheral sensory neurons.

PKCε has a crucial role in sensitizing peripheral neurons to painful stimuli leading to the sensitization of transient receptor potential vanilloid 1 (TRPV1) and other nociceptor specific ion channels. Translocation can be easily visualized with immunocytochemistry[42-46]. Inhibition of translocation by nimesulide and paracetamol to a lesser extent has been recently proposed as a novel analgesic mechanism activated by these drugs. [7] opined that In sensory neurons, the activation of PKCε by inflammatory mediators (or, artificially, by phorbol esters) is followed by its translocation to the plasma membrane. In this study, PKCε activation was quantified as the percentage of neurons showing membrane translocation. Following exposure to 100nM THR or 1μM BK, sufficient to saturate the specific receptors, maximum translocation was always observed [44,47]. Application times longer than 30 seconds would allow PKCε to become internalized into perinuclear vesicles, decreasing the number of translocation-positive neurons, as has been shown previously [44,47]. As maximum percentage of translocation was reliably measured at 30 seconds of exposure to the agonist concentrations mentioned, as in previous studies [9] these parameters were used for most of the work, with the exception of some experiments with nimesulide and paracetamol, in which the researcher tested a roughly half-maximal agonist concentration (10nM applied for 30 seconds in the case of both stimulants) [44,47]. THR applied on cultures for 30 seconds at 100nM and BK applied on cultures for 30 seconds at 1μM, triggered translocation in 17.8% ± 1.0% and 26.3% ± 1.2% of DRG neurons respectively, in this set of experiments, a percentage similar to that previously obtained [7] THR and BK applied for 30 seconds at 10nM triggered translocation in 8.8% ± 0.9% and in 14.4% ± 0.7% of DRG neurons respectively.

Paracetamol (10μM), also as previously observed,[7]inhibited translocation by 100nM THR and 1μM BK to 13.4% ± 0.5% and 16.6% ± 0.7%, respectively, with a reduction of ~25% and ~37%, respectively. A larger concentration of paracetamol (100μM) was tested on translocation by 100nM THR and 1μM BK causing a reduction of ~27% and ~34%, respectively, versus the respective controls. It was concluded that the maximal paracetamol effect on translocation was achieved at a concentration of 10μM.

SP – a neuropeptide derived from the preprotachykinin (PPT)-A gene produced in a subset of peptidergic nociceptive neurons located in the dorsal root ganglia (DRGs) and trigeminal ganglia is required for experiencing moderate to intense pain [48]. Centrally, SP is released in the superficial laminae of the spinal dorsal horn, where it participates in the transmission of noxious stimuli [49]. Concentrations of SP released by cultured sensory neurons in culture medium were measured by RIA. After 24 hours in culture, individual coverslips from the same cultures were treated either with

vehicle or IS. Separate IS-treated coverslips contained either one of the NSAIDs investigated, paracetamol (all at 10 μM) or vehicle solution, giving a total of seven conditions. all results shown are normalized to basal (vehicle-only) levels, nimesulide was the only compound found to be capable of significantly reducing SP release. At 36 hours following exposure to the IS, nimesulide, celecoxib, and diclofenac significantly reduced the IS-induced release of SP, while reductions caused by paracetamol and ibuprofen were not statistically significant. Paracetamol was also tested at a concentration of 100 μM,at this concentration, paracetamol did not significantly reduce stimulated SP release in medium at 70 minutes or 36 hours. Therefore, it can be said that modulation of protein kinase C epsilon (PKCε) and substance P (SP) in the peripheral sensory neurons may be partly responsible for analgesic mechanism of action of acetaminophen [7].

Table 1 Summary of the mechanism of action of Acetaminophen

Acetaminophen compound	Target site	Effect/ mechanism	Reference
AM404	TRPV-1	Activating	[19]
AM404	CB1 receptors	Activating	[20]
AM404	Cav3.2	Inhibitory	[4]
Acetaminophen	Cav3.2	No effect	[26]
Acetaminophen / AM404	5-HT_2, 1,1_A,$1_{B,3,7}$	Activate	[31,6]
Acetaminophen	Nitric Oxide	Inhibition	[37]
Acetaminophen	Opoids(mu, delta and kappa)	Activate	[41]
Acetaminophen	Protein Kinase C epsilon (PKCε) and Substance P(SP)	Activation	[7]

4. Conclusion

Findings in the last decade related to the contribution of some receptors and neurotransmitter as implicated in the analgesic mechanism of action of acetaminophen. Recent studies confirmed involvement in acetaminophen, metabolized by fatty acid amide hydrolase (FAAH) to yield N-acylphenolamine (AM404). AM404 produced analgesic action by acting on several receptors like the transient receptor potential vanilloid-1 (TRPV1) and cannabinoid 1 (CB1) receptors in the midbrain and medulla and acetaminophen-induced serotonin increases in the central nervous system. The metabolite AM404, contributes to the analgesic effect of acetaminophen, increasing serotonin neurotransmission (receptor) subtypes also contribute to the antinociceptive actions of acetaminophen and suppression of the central Nitric oxide (NO) systems is also involved in the central analgesic mechanisms of acetaminophen. Moreover the analgesic effects of acetaminophen were attenuated by mu-,delta-, and kappa-opioid receptor antagonists which is indicative that activation of opoid receptors induced analgesia. PKCε and SP activation was also proven to be responsible for acetaminophen analgesic mechanism of action. These findings thus far would be invaluable to health personnel especially clinicians who are involved in pain management. Pharmacology teachers will also find the review a useful one, although the analgesic mechanisms of action of is yet to be specifically explicit.

Compliance with ethical standards

Acknowledgments

The authors are grateful to the Prof Prince Unekwe of Department of Pharmacology and Therapeutics, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University, Nnewi Campus, for a conducive research environment.

Disclosure of conflict of interest

No conflict of interest was declared by the authors.

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