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Review

Acetaminophen from liver to brain: New insights into drug pharmacological action and toxicity

Carolina I. Ghanem[a,b,*], María J. Pérez[c], José E. Manautou[d], Aldo D. Mottino[e]

[a] Instituto de Investigaciones Farmacológicas (ININFA), Facultad de Farmacia y Bioquímica, CONICET, Universidad de Buenos Aires, Buenos Aires, Argentina
[b] Cátedra de Fisiopatología, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina
[c] Cátedra de Química Biológica Patológica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Instituto de Química y Fisicoquímica Biológica (IQUIFIB), UBA—CONICET, Buenos Aires, Argentina
[d] Department of Pharmaceutical Sciences, University of Connecticut, Storrs, CT, United States
[e] Instituto de Fisiología Experimental (IFISE), Facultad de Ciencias Bioquímicas y Farmacéuticas, CONICET, Universidad Nacional de Rosario, Rosario, Santa Fe, Argentina

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ABSTRACT

Acetaminophen (APAP) is a well-known analgesic and antipyretic drug. It is considered to be safe when administered within its therapeutic range, but in cases of acute intoxication, hepatotoxicity can occur. APAP overdose is the leading cause of acute liver failure in the northern hemisphere. Historically, studies on APAP toxicity have been focused on liver, with alterations in brain function attributed to secondary effects of acute liver failure. However, in the last decade the pharmacological mechanism of APAP as a cannabinoid system modulator has been documented and some articles have reported "in situ" toxicity by APAP in brain tissue at high doses. Paradoxically, low doses of APAP have been reported to produce the opposite, neuroprotective effects. In this paper we present a comprehensive, up-to-date overview of hepatic toxicity as well as a thorough review of both toxic and beneficial effects of APAP in brain.

Contents

Abbreviations: AEA, anandamide; AM404, *N*-arachidinoyl-phenolamine; AMAP, 3′-hydroxyacetanalide; AMT, anandamide membrane transporter; ALF, acute liver failure; APAF-1, apoptosis protease-activating factor-1; APAP, acetaminophen; ATP, adenosine triphosphate; CAR, constitutive androstane receptor; CB, cannabinods receptors; CNS, central nervous system; COXs, cyclooxygenase; CYP, cytochrome P-450 isoenzymesmixed-function oxidase system; DAMPs, damage-associated molecular pattern molecules; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum; FAAH, fatty acid amide hydrolase; GSH, glutathione; GSSG, glutathione disulfide; HE, hepatic encephalopathy; HIF-1α, hypoxia-inducible factors; HMGB1, high mobility group box-1; Ho-1, hemeoxygenase; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein; ECH, associated protein; KO, knock-out; MAPK, mitogen-activated; MLKL, mixed lineage kinase like is produce; MPT, membrane permeability transition; NAC, *N* acetyl-cysteine; NAPQI, *N*-acetyl-*p*-benzoquinoneimine; Nec, necrostatins; NO, nitric oxide; Nqo1, NAD(P)H dehydrogenase, quinone 1; Nrf2, nuclear factor erythroid 2-related factor 2; NSADs, nonsteroidal anti-inflammatory drugs; PINK1, phosphatase and tensin homolog (PTEN)-induced kinase 1; RIPK, receptor interacting protein kinase; ROS, reactive oxygen species; Sab, Src homology 3 domain binding protein 5; TBP, TATA-binding protein; TRPV1, vanilloid subtype 1 receptors; WT, wild type; XBP1, X-box binding protein-1; 4-PBA, sodium 4-phenylbutyrate.

* Corresponding author at: Instituto de Investigaciones Farmacológicas (ININFA), Facultad de Farmacia y Bioquímica, Junín 953, 5to. piso, Buenos Aires C1113AAD, Argentina.
E-mail address: cghanem@ffyb.uba.ar (C.I. Ghanem).

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1. Introduction

Acetaminophen (*N*-acetyl-*para*-aminophenol, paracetamol, APAP) was originally synthesized in 1878 by Morse [1] and first used clinically by von Mering in 1887 [2]. During that period, phenacetin was the most widely used analgesic in clinical practice. In the 1950s, the analgesic and antipyretic properties of APAP were re-discovered by Brodie and Axelrod [3] and they demonstrated that APAP was in fact the active metabolite of phenacetin. At that time, APAP was introduced in the U. S. market as a replacement drug for phenacetin, whose use was discontinued due to its nephrotoxic potential. Owing to its widespread acceptance as a safer alternative to phenacetin, APAP became one of the most popular and widely used over-the-counter analgesic-antipyretic drugs in the world, and the most commonly prescribed medication in children [4,5]. Also, since the 1980's APAP has become the first drug of choice for the treatment of pain and fever in children because of the high incidence of Reye's syndrome associated with pediatric use of aspirin [6]. In the U.S., approximately 79% of the general population consume APAP regularly [7]. Many prescription and nonprescription formulations contain APAP alone or in combination with other drugs. Excessive self-medication is a prevalent practice responsible for many cases of APAP intoxication.

2. An update on the mechanism(s) of pharmacological action

Historically, APAP was initially categorized as a nonsteroidal anti-inflammatory drugs (NSADs). Multiple investigations compared its mechanism of action to that of classical NSAIDs, such as acetyl salicylic acid which inhibits the cyclooxygenase (COXs) pathway [8]. However, APAP was proven to be ineffective as an anti-inflammatory drug. It is well established that NSAIDs inhibit COX-dependent production of prostaglandins [9], while

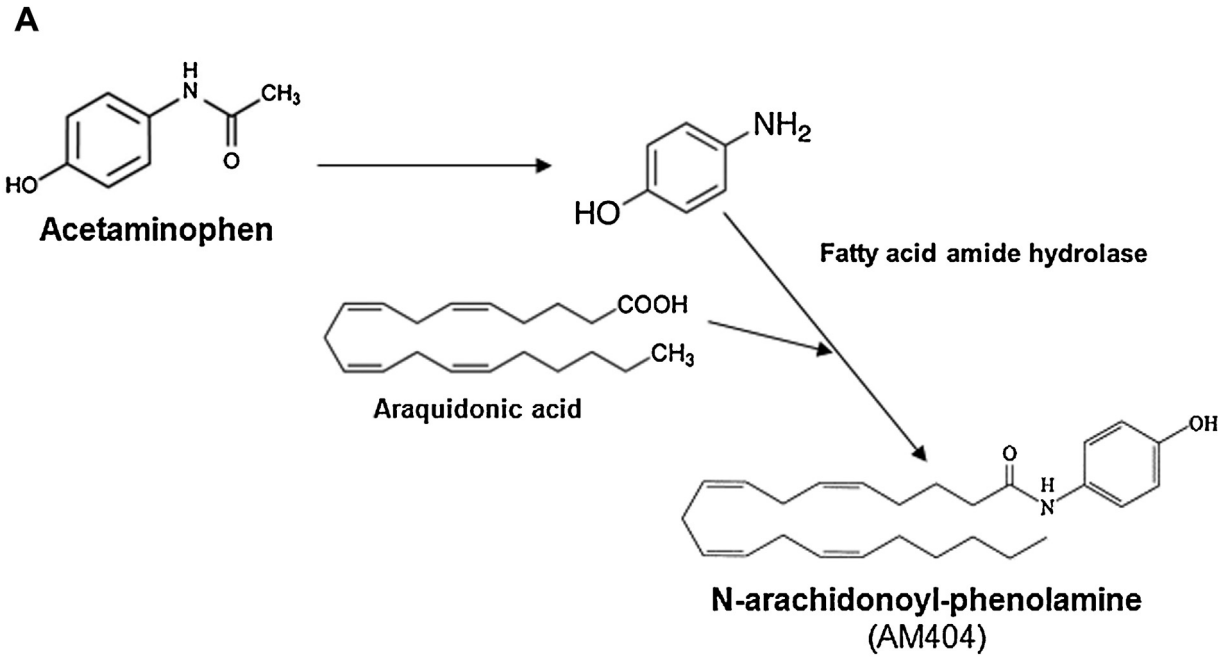

Fig. 1. FAAH-metabolite of APAP: generation of *N*-arachidonoyl-phenolamine (AM404) in brain. **Panel A**: APAP is deacetylated followed by the formation of AM404 by the addition of arachidonic acid, which is catalyzed by fatty acid amide hydrolase (FAAH) in brain. **Panel B**: structures of AM404 and anandamide.