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Induction of prostaglandin-endoperoxide synthase 2 by mitogen-activated protein kinase cascades - Review of the evidence

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ONLINE ARTICLE

ARTICLE INFORMATION

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1. ABSTRACT

The analyzed study evaluated whether three families of proteins involved in intracellular signal transmission, the MAPKs (mitogen-activated protein kinases), can induce COX-2 expression. The authors experimentally activated the ERK, JNK, and p38 pathways in cell lines and observed an increase in messenger RNA and the COX-2 protein. The available material is only the abstract: it does not report the precise cell type, the number of experiments, quantitative values, nor a measurement of prostaglandin E2 (PGE2).In paragraph 5.5.1 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes primarily to the MAPK → COX-2 induction segment. It does not directly document that insulin induces this sequence, nor that MAPK activation increases PGE2 in its model. However, independent research shows that, in different cellular and animal contexts, MAPK activation can increase COX-2 and PGE2. The evidence therefore supports the mechanism at an experimental level, while the extension to an effect of chronic insulin in humans requires specific confirmation.

MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

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2. ANALYZED STUDY

The research question was whether the three main MAPK pathways can increase the expression of prostaglandin-endoperoxide synthase 2, now commonly called COX-2 or cyclooxygenase-2. COX-2 is an inducible enzyme: in many cells, it appears or increases when growth, stress, or inflammation signals arrive. Its biological significance is relevant because it transforms free arachidonic acid into prostanoid intermediates from which various prostaglandins and thromboxanes are derived.The relevance to section 5.5.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns the passage stating that the activation of MAPK pathways can induce COX-2. The study verified this hypothesis in cell systems artificially modified to maintain specific signaling pathways active. It can therefore demonstrate a causal relationship between the experimental activation of MAPKs and the increase of COX-2 in the model used. However, it cannot demonstrate that insulin was the initial signal, that the phenomenon occurs in all human tissues, or that the increase in COX-2 directly produced PGE2, as this latter measurement is not reported in the available abstract.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study is experimental and conducted in cell lines. To activate the ERK pathway, the authors used constitutively active forms of MEK1, a protein located upstream of ERK. The expression of active MEK1 was achieved both in stably modified cells and through infection with adenoviral vectors, which are tools used to temporarily introduce a gene into cells.To examine JNK and p38-MAPK, the authors transferred active forms of the respective upstream regulatory proteins via adenovirus: MKK7 for JNK and MKK3/MKK6 for p38. The variables analyzed were the expression of COX-2 messenger RNA and the COX-2 protein. The number of cell lines, their names, the number of biological replicates, observation times, doses or quantities of the vectors, specific analytical methods, and statistical analyses are not reported in the available material.The abstract does not describe a control group in detail, but the implicit comparison is between cells in which the pathways under consideration were activated and non-activated cellular conditions. No direct measurements of arachidonic acid, prostaglandin H2, PGE2, COX-2 enzymatic activity, or other products of the prostaglandin pathway are reported.

4. RESULTS

The main result is that the activation of the ERK pathway increased messenger RNA and the COX-2 protein. In simple terms, when the ERK signal was artificially kept on, the cells produced more genetic instructions for COX-2 and more COX-2 enzyme.An increase of the same type was also observed after the experimental activation of the JNK pathway via MKK7 and the p38-MAPK pathway via MKK3b or MKK6b. The authors therefore conclude that all three main mammalian MAPK cascades can induce COX-2 expression. This conclusion applies to both the messenger RNA level and the protein level.The available material does not report absolute values, percentage variations, confidence intervals, P-values, or experimental sample sizes. It also does not report a measured increase in PGE2. It is therefore correct to state that the study documents MAPK increase in messenger RNA and COX-2 protein; it is not correct to attribute to it the direct demonstration of MAPK increase in PGE2.

5. INTERPRETATION

The result suggests that very different signals can converge on a common point: the activation of MAPK and the increase in cellular availability of COX-2. In layman's terms, ERK, JNK, and p38 can be considered three internal cell communication pathways that, when activated, increase the production of an enzyme capable of initiating the formation of prostanoids from arachidonic acid.This is the segment of the narrative that the publication directly documents: the activation of ERK, JNK, or p38 is sufficient, in the cells studied, to increase COX-2. However, the subsequent biochemical step requires clarification. COX-2 does not directly convert arachidonic acid into PGE2: it first produces the intermediates prostaglandin G2 and prostaglandin H2; PGE2 is then formed by specific PGE synthases. Saying that COX-2 makes the production of PGE2 possible is a reasonable functional simplification, but the actual amount of PGE2 also depends on the presence of other enzymes, the tissue,

and the stimulus.Consequently, the study analyzed causally supports the MAPK COX-2 pathway, but not the entire insulin arachidonic acid COX-2 PGE2 sequence. In particular, insulin was not studied, and PGE2 production is not reported in the available material.

6. INDEPENDENT SUPPORTING EVIDENCE

Particularly relevant independent confirmation comes from a study on immortalized human chondrocytes, which are cartilage cells. Following stimulation with interleukin-1b, an inflammatory molecule, ERK1/2, p38, and JNK were activated; this activation was followed by an increase in COX-2 and an increase in PGE2 in the culture medium. Inhibitors of the three pathways reduced COX-2 and PGE2 in a concentration-dependent manner. For p38 and ERK, the reduction of COX-2 messenger RNA was evident early on, while for JNK it was delayed, suggesting that the mechanisms among the three pathways are not identical. The study confirms, in human cells but not in people, that MAPK COX-2 can be accompanied by COX-2 increase in PGE2 [1].In an animal model of trauma, spleen macrophages isolated from mice seven days after the injury showed increases in COX-2 messenger RNA and protein, along with greater PGE2 production compared to controls. In the same cells, the phosphorylation—that is, the regulatory activation—of ERK and JNK increased. Pharmacological inhibition of MAPK blocked both the increase in COX-2 and the production of PGE2. This study reinforces the MAPK COX-2 PGE2 chain in a complex inflammatory context, but the model is murine and also involves the activation of NF-kB, another regulator of the inflammatory response [2].Further confirmation of the ERK COX-2 PGE2 axis was obtained in primary microglia, which are resident immune cells of the nervous system. Experimental reduction of the TDP-43 protein increased the phosphorylation of MEK and ERK, COX-2, and the release of PGE2; the MEK inhibitor prevented the increase in COX-2, while celecoxib reduced PGE2 production. The medium from the modified microglia increased neuron death in culture. This research shows a biological consequence downstream of the axis, but it concerns a model of neuroinflammation and does not demonstrate a systemic metabolic or insulin effect [3].Taken together, these independent studies do not exactly replicate the design of the analyzed publication, but they converge on the same biological core: MAPK activation can increase COX-2 and, in contexts where the appropriate terminal enzymes are present, can be accompanied by greater PGE2 production. The confirmation is experimental and mechanistic; it does not derive from clinical studies that directly link chronic insulin to PGE2 through this sequence.

7. CONFLICTING EVIDENCE

Available evidence indicates that the effects of the arachidonic acid–COX-2–PGE2 axis are highly tissue-dependent. In isolated human pancreatic islets, COX-2 inhibition with NS-398 increased basal insulin secretion and the secretory response to glucose or arachidonic acid. However, the addition of PGE2 did not significantly reduce glucose-stimulated insulin secretion under static conditions and increased basal secretion. This does not contradict the induction of COX-2 by MAPKs, but it shows that PGE2 cannot be attributed a single, invariably pro-inflammatory or unfavorable effect in every human tissue [4].There is also a methodological limitation in research that uses only pharmacological MAPK inhibitors: some compounds used historically can directly influence cyclooxygenase activity, making it more difficult to separate the effect on intracellular signaling from that on the final enzyme. The analyzed publication reduces this problem because it genetically activated upstream pathways, but confirmations based on inhibitors must be interpreted with caution. No directly conflicting evidence sufficiently relevant to the central result of the original study—namely, the increase in COX-2 after experimental activation of MAPKs—has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the study that is the subject of the Evidence Review from the independent publications used to confirm or define the biological chain.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Experimental cellular	Cell lines with artificial activation of ERK, JNK, or p38	Activation of the three MAPK pathways increases COX-2 messenger RNA and protein; PGE2 not measured in available material.	direct confirmation	moderate
[1]	Cellular	Immortalized human T/C28a2 chondrocytes stimulated with interleukin-1b	Activation of ERK, p38, and JNK followed by an increase in COX-2 and PGE2; inhibitors reduce both.	direct confirmation	moderate
[2]	Animal and ex vivo cellular	Splenic macrophages from mice subjected to trauma	Trauma associated with increased ERK, JNK, p38, COX-2, and PGE2; inhibiting MAPK reduces COX-2 and PGE2.	direct confirmation	moderate
[3]	Cellular	Primary microglia and neurons in culture	ERK activation increases COX-2 and PGE2; reduction of COX-2/PGE2 attenuates neurotoxicity in the model.	biologically consistent evidence	low
[4]	Ex vivo cellular	Isolated human pancreatic islets	COX-2 inhibition increases insulin secretion; PGE2 does not significantly reduce glucose-induced secretion.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed study directly supports the claim that the experimental activation of ERK, JNK, and p38 can increase COX-2 expression. This is the specific reason why the publication is relevant to the section of the paragraph dedicated to the regulation of the prostaglandin axis.Independent evidence confirms at a mechanistic level that, in multiple experimental models, MAPK can increase COX-2 and be accompanied by increased PGE2 production. However, the conclusion must remain limited: the original study does not measure PGE2, does not study insulin, and does not allow for the automatic transfer of this mechanism to all human tissues or to systemic inflammation.The narrative is therefore well-supported for the MAPK COX-2 cellular segment and moderately completed for the COX-2 PGE2 segment. The entire sequence starting from chronic insulin requires specific validation in humans.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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