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Insulin activates microglia and increases COX-2/IL-1b expression in the young hippocampus but not in the aged one - Evidence review

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1. ABSTRACT

The analyzed study evaluated whether insulin administered to the brain can modify microglia, the resident immune cells of the central nervous system, in the hippocampus of young and aged rats. In young rats, repeated insulin exposure increased markers of microglial activation and levels of COX-2 and IL-1b; in aged rats, these increases were not significant. In primary microglial cultures, insulin also increased the phosphorylation of AKT, an intracellular signal associated with the insulin receptor.In section 5.5 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the publication contributes to the premise that insulin can induce COX-2 in microglia, an enzyme necessary for prostaglandin synthesis. Independent evidence supports that hyperinsulinemia can promote a pro-inflammatory microglial profile and that, in microglia, the increase in COX-2 can be accompanied by greater PGE2 production. However, the specific link insulin → MAPK-ERK → COX-2 → PGE2 is not fully demonstrated by the original study nor confirmed in humans.

ONLINE ARTICLE

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2. ANALYZED STUDY

The research question was whether insulin can modify the activation state of microglia in the hippocampus and whether this response changes with age. The hypothesis was that insulin signaling could integrate with inflammatory signals in the brain's immune cells. The topic is relevant because microglia can produce mediators that influence the nervous environment; however, their activation does not automatically equate to neurological damage.The relevance to section 5.5 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi concerns a specific segment of the proposed chain: insulin can be associated with an increase in COX-2 in microglia or in the hippocampal tissue that contains it. COX-2, or cyclooxygenase-2, is an enzyme that participates in the transformation of arachidonic acid into prostaglandin precursors, including prostaglandin E2. The study did not directly measure the production of PGE2, did not verify the MAPK-ERK pathway, and does not allow for the transfer of these results to healthy or sick individuals.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract; therefore, information not included in the abstract must be considered as not reported in the available material. The researchers administered insulin or a control vehicle intracerebroventricularly—that is, directly into the cerebral ventricles—for five days. The indicated dose was 20 mU. The study involved 3-month-old young Wistar rats and 22-month-old aged rats.In the hippocampus, markers of microglial activation identified as Iba-1 positive and CD68 positive cells were evaluated, along with levels of COX-2 and interleukin-1b, or IL-1b, a protein involved in inflammatory responses. For the young rats, an assessment was also scheduled eight days after the final administration, along with a spatial memory test, the Morris Water Maze. In primary microglia cultures, the phosphorylation of AKT at Ser473 was evaluated, a chemical modification that signals the activation of an intracellular pathway linked to the insulin receptor.The sample size of the groups, inclusion and exclusion criteria, method of treatment assignment, randomization and blinding procedures, complete analytical techniques, detailed statistical analyses, and numerical values of the results are not reported in the available material.

4. RESULTS

In young rats, five days of intracerebral insulin increased the number of microglia with Iba-1 and CD68 markers in the hippocampus and raised levels of COX-2 and IL-1b compared to the vehicle. In simple terms, the treatment was accompanied by a change in brain immune cells and an increase in two indicators consistent with an inflammatory response. The abstract does not report absolute values, percentage changes, confidence intervals, or P-values for these comparisons.In older rats, the same insulin exposure did not produce a significant increase in Iba-1 positive and CD68 positive microglia, nor in COX-2 and IL-1b levels. Eight days after the last administration, microglial activation and the increase in COX-2 were still present in young rats; this trend was accompanied by better performance in the spatial memory test. This temporal parallelism does not prove that COX-2, activated microglia, or insulin caused the memory improvement.In primary microglia, insulin increased the phosphorylation of AKT at Ser473. This result shows that these cells can respond directly to insulin signaling. However, it does not prove that AKT is responsible for the increase in COX-2 observed in the living hippocampus, nor that MAPK-ERK or PGE2 production are involved.

5. INTERPRETATION

The main significance is that, in the experimental model used, insulin administered repeatedly into the brains of young rats was associated with an increase in microglial markers and COX-2 in the hippocampus. Since COX-2 contributes to the production of prostanoids, this observation makes it biologically plausible that insulin signaling may contribute to the predisposition of a local pro-inflammatory environment.The segment documented by the publication subject to the Evidence Review is therefore: insulin in the central nervous system microglial activation and increased COX-2 in the hippocampus of young rats. The book proposes a broader chain, in which insulin activates MAPK-ERK and induces COX-2, predisposing the conversion of arachidonic acid into PGE2. The original study does

not measure MAPK-ERK, free arachidonic acid, cPLA2a, mPGES-1, PGE2, or the biochemical flux between these steps.Furthermore, the different result in older rats indicates that the response is not universal: age, baseline inflammatory status, and cerebral insulin resistance can modify the effect. The research therefore offers relevant but limited experimental evidence, not a complete demonstration of the sequence proposed in the book's paragraph.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the first step—that excess insulin signaling can promote a pro-inflammatory microglial profile—comes from a mouse model of diet-induced insulin resistance and from experiments on primary microglia and BV2 cells. In mice, the diet increased insulin levels in the blood and cerebrospinal fluid, which was accompanied by hippocampal microglial activation and increased IL-1b. In cultures, insulin increased microglial proliferation, markers of pro-inflammatory polarization, and cytokine production. The study did not measure COX-2 or PGE2 as primary endpoints; therefore, it confirms the insulin pro-inflammatory microglial response link, but not the entire lipid chain described in the book [1].A second study, conducted on primary rat microglia, clarifies the downstream step: when microglia are stimulated with poly(I:C), an experimental viral RNA analog, they increase COX-2, mPGES-1, and PGE2 release. Inhibition of MEK1/2, an enzyme upstream of ERK, reduced the increase in COX-2 and mPGES-1. This supports the idea that in microglia, a pathway involving MEK-ERK may help link an inflammatory stimulus to the enzymatic apparatus that produces PGE2. The stimulus was not insulin; therefore, confirmation of the insulin link remains indirect.In another primary rat microglia model, the bacterial stimulus LPS increased COX-2 and PGE2 synthesis. Here, however, the crucial signal was found to be p38 MAPK rather than the ERK1/2 pathway. The study confirms in a biologically consistent manner that the induction of COX-2 in microglia can translate into increased PGE2, but it also signals that the prevalent kinase depends on the stimulus and the experimental context [2].An experiment on BV2 cells showed that insulin added after LPS increased nitric oxide, TNF, and IL-6 via AKT/NF-kB, while reducing intracellular oxidative stress. The authors did not identify MAPK-ERK as a mediator of the insulin effect and did not measure COX-2 or PGE2. This result is important because it indicates that insulin can simultaneously increase certain inflammatory responses and reduce certain oxidative components, making a univocal representation of its effect on microglia inappropriate [3].

7. CONFLICTING EVIDENCE

There is directly relevant evidence that calls for caution regarding the obligatory role of MAPK-ERK. In primary microglia stimulated with LPS, the increase in COX-2 and PGE2 was dependent on p38 MAPK and not on ERK1/2; therefore, COX-2 can be induced in microglia through MAPK pathways other than ERK [2]. This does not refute the possibility that MEK-ERK may contribute in other contexts, but it shows that it cannot be considered the sole regulatory pathway.In BV2 cells already activated by LPS, insulin enhanced the production of certain pro-inflammatory cytokines via AKT/NF-kB, but reduced reactive oxygen species and NADPH oxidase activity. The direction of the effect therefore depends on the indicator observed: an increase for some immune mediators, a reduction for some oxidative signals [3]. No directly conflicting evidence of sufficient relevance has been identified regarding the exact effect of repeated intracerebral insulin on hippocampal COX-2 levels in young rats; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the results of the original study from independent publications that confirm or define specific steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	Young and aged Wistar rats; primary microglia	Intracerebral insulin increased microglial activation, COX-2, and IL-1b in the young hippocampus, but not in the aged one.	direct confirmation	moderate
[1]	Animal and cellular	Mice with diet-induced insulin resistance; primary microglia and BV2	Hyperinsulinemia and insulin treatment increased pro-inflammatory markers and pro-inflammatory microglial polarization.	indirect confirmation	moderate
	Cellular	Rat primary microglia stimulated with poly(I:C)	The increase in COX-2 and mPGES-1 was associated with higher PGE2 and was reduced by MEK inhibitors.	biologically consistent evidence	moderate
[2], [3]	Cellular	Rat primary microglia stimulated with LPS; BV2 cells treated with LPS and insulin	COX-2/PGE2 may depend on p38 MAPK rather than ERK; insulin may increase cytokines but reduce oxidative stress.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed provides experimental support for the fact that insulin administered repeatedly into the brains of young rats can increase microglial activation and hippocampal levels of COX-2 and IL-1b. This makes its inclusion relevant in the section dedicated to COX-2 induction.The subsequent part of the narrative, namely the link to PGE2, is supported at a mechanistic level by independent studies on microglia. However, the MAPK-ERK pathway does not appear to be unique, nor is it directly demonstrated as a mediator of the insulin effect in the original study. The entire sequence therefore remains a biologically plausible reconstruction that is moderately supported by experimental models and requires 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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