# Metformin reverses cognitive impairment and knee oxidative damage in a model of osteoarthritic pain

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## Background and aims

- **Osteoarthritis** (OA) is a **highly prevalent chronic rheumatic disease**, characterized by cartilage loss with consequent **joint pain and dysfunction** (most commonly of the knees) [1].
- Even though it is primarily a joint disorder, OA can have **substantial extra-articular complications**, including increased risk of **cognitive decline** [2].
- Despite its high prevalence, **currently no drug has been approved as a disease-modifying therapy**, and most available treatment options only alleviate joint pain [1,3].
- In recent years, **metformin** (a well-known antidiabetic drug) has been shown to be effective in relieving pain and preventing cartilage loss in OA in preclinical and human studies [3].

We aimed to expand the existing data on the effects of **metformin (MET) in OA**, and examine its effects on **pain-related behavior, extra-articular manifestations (cognitive performance) and level of joint oxidative damage in a model of OA.**

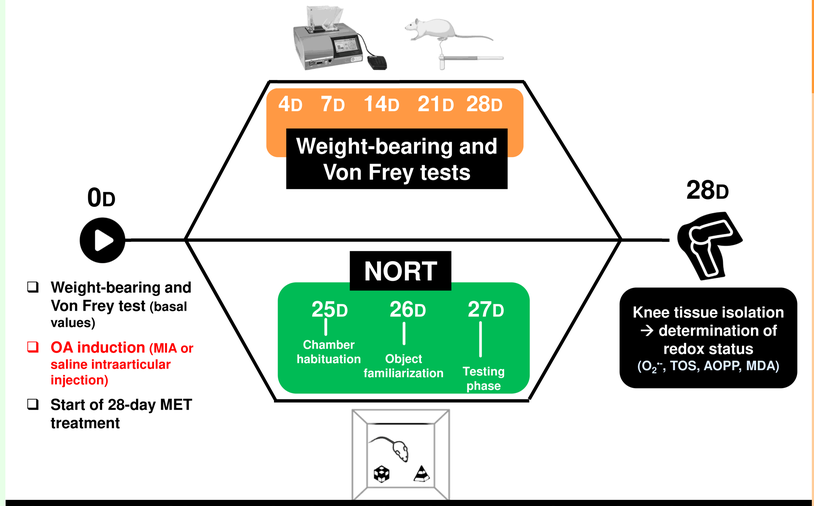


**Fig. 1. Protocol for examination of the effects of prolonged metformin (MET) treatment in the model of osteoarthritis (OA) induced with MIA.**

## Methods

- OA was induced in **male and female Wistar rats** with an **intraarticular injection of sodium monoiodoacetate (MIA; Figure 1)**. Saline-control rats received an intraarticular injection of saline [4].
- Rats received MET (100 mg/kg/day orally) for 28 days.
- Different tests were used to assess pain-related behavior and cognitive performance.
- **Pain-related behavior**: weight-bearing and Von Frey tests (assessment of weight-bearing asymmetry and mechanical hypersensitivity, respectively).
- **Cognitive performance**: novel object recognition test (NORT).
- After the 28-day period, **knee tissue** was collected for **determination of oxidative stress parameters**: superoxide anion radicals ($O_2^{\bullet-}$), total pro-oxidant status (TOS), advanced oxidation protein products (AOPP) and malondialdehyde (MDA).

## Results

### Pain-related behavior

- **Intraarticular MIA produced significant weight-bearing asymmetry and mechanical hypersensitivity in rats of both sexes** ($P < 0.001$ *vs* saline-controls; Figure 2).
- **MET treatment reduced weight bearing asymmetry and mechanical hypersensitivity in male and female rats** ($P \leq 0.008$ *vs* MIA-controls; Figure 2).

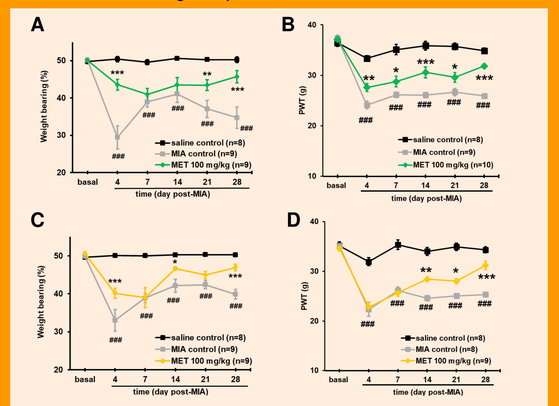


**Fig. 2. MET reduces weight-bearing asymmetry and mechanical pain hypersensitivity in rats with MIA-induced OA.**
Results from the weight-bearing test are on panels A and C, and from the Von Frey test on panels B and D. Results for male and female rats are represented with green and orange coloring, respectively. Statistical significance was determined in comparison with the saline (###$P < 0.001$) or MIA control (*$P <$ 0.05, **$P < 0.01$, ***$P < 0.001$) with 2-way repeated measures ANOVA (Tukey *post-hoc* test)

### Novel-object recognition test

- **In NORT, OA induction impaired cognitive performance**, i.e. discrimination indexes of male and female MIA-controls were significantly lower compared to saline-controls ($P \leq 0.002$; Figure 3).
- **MET reversed OA-induced cognitive deficits in NORT,** and significantly increased discrimination indexes in rats of both sexes ($P \leq$ 0.033 *vs* MIA-controls; Figure 3).

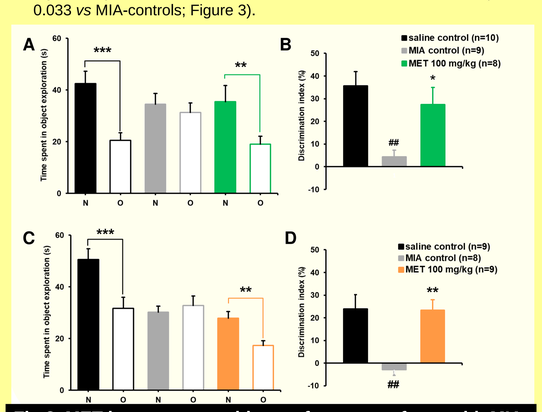


**Fig 3. MET improves cognitive performance of rats with MIA-induced OA.**
Results are presented as time spent exploring the novel (N) and old (O) object (A and C) and discrimination indexes (B and D). Results for male and female rats are represented with green and orange coloring, respectively. Time spent in exploring the N and O object was analyzed using 2-way ANOVA (**$P < 0.01$, ***$P < 0.01$; Tukey *post-hoc* test) and the differences between discrimination indexes were analyzed with 1-way ANOVA (##$P < 0.01$ *vs.* saline control; *$P < 0.05$, **$P < 0.01$ *vs.* MIA control; Tukey *post-hoc* test).

### Knee redox status

- **All parameters of knee oxidative damage were significantly increased in male and female rats with OA** ($P \leq 0.049$ *vs* saline-controls; Figure 4).
- **MET significantly reduced $O_2^{\bullet-}$, TOS, AOPP and MDA levels in male rats** ($P \leq 0.041$ *vs* MIA-controls; Figure 4), whereas **in female rats it significantly reduced TOS, AOPP and MDA** ($P \leq 0.009$ *vs* MIA-controls), but not $O_2^{\bullet-}$.

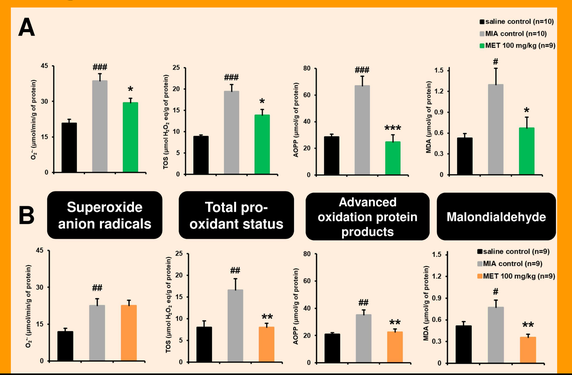


**Fig 4. MET reduces oxidative stress markers in knee tissue of rats with MIA-induced OA.**
Results for male and female rats are represented with green and orange coloring, respectively. The levels of oxidative stress markers were determined after prolonged (28 days) administration of MET. Statistical significance was determined in comparison with the saline (#$P < 0.05$, ##$P < 0.01$; ###$P < 0.001$) or MIA control group (*$P < 0.05$, **$P < 0.01$; ***$P < 0.001$) with 1-way ANOVA (Tukey *post-hoc* test).

## Conclusion

- **Prolonged MET treatment produced several beneficial effects in male and female rats with OA.**
- MET was capable of **alleviating pain-related behavior** (weight-bearing asymmetry and mechanical hypersensitivity).
- MET was **effective in reversing cognitive impairment** of rats with OA, which indicates its potential utility in relieving extra-articular complications of OA.
- MET **reduced the level of oxidative damage of knee tissue** in rats with OA. These findings suggest that anti-oxidative effects could be an additional mechanism contributing to metformin's disease-modifying properties.

**References:**
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