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## Do Endorphins Mediate Placebo Analgesia? A Critical Commentary on One of the Seminal Papers

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### Key Words

Analgesia · Double-blind method · Endorphin antagonists and inhibitors · Placebos · Random allocation

### Summary

There are only few experimental studies that assess the hypothesis that placebo analgesia is mediated by endogenous opioids. One of these studies [Grevert P, Albert LH, Goldstein A: Partial antagonism of placebo analgesia by naloxone. *Pain* 1983;16:129-143] had a rather complicated design and data presentation. In this commentary we attempt to clarify the experimental design of that study. Based on a clearer understanding of the study procedures and data analysis we propose some alternative interpretations of the results.

### Schlüsselwörter

Analgesie · Doppelblind-Methode · Endorphinantagonisten und -inhibitoren · Placebos · Zufallszuteilung

### Zusammenfassung

*Sind Endorphine die Erklärung für die Placebo-Wirkung bei Schmerzen? Ein kritischer Kommentar einer aufschlussreichen Publikation*

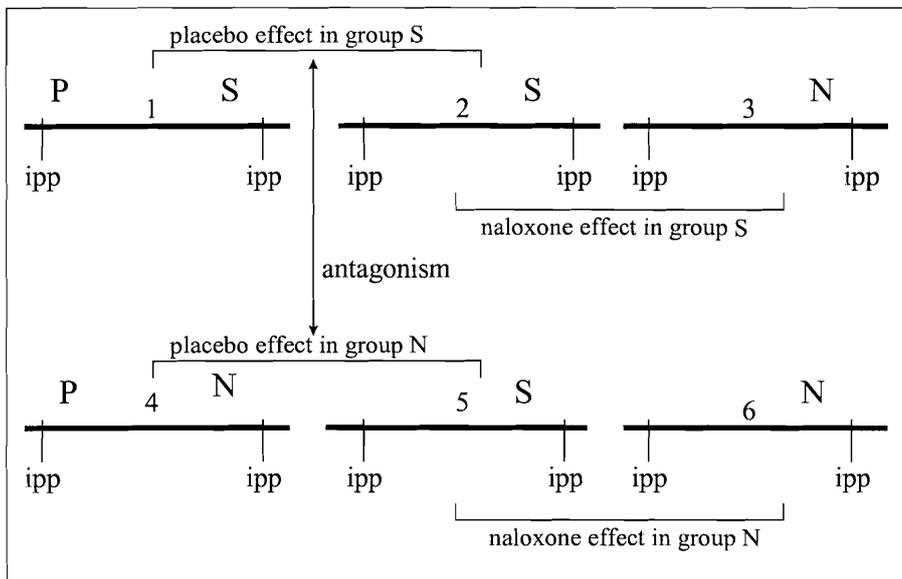
Es gibt nur wenige experimentelle Studien, die sich mit der Hypothese beschäftigen, dass die placebobedingte Analgesie durch endogene Opiode vermittelt wird. Bei einer dieser Studien [Grevert P, Albert LH, Goldstein A: Partial antagonism of placebo analgesia by naloxone. *Pain* 1983;16:129-143] waren Design und Präsentation der Daten aber ziemlich kompliziert. Ziel dieses Kommentars ist es, das experimentelle Design dieser Studie aufzuklären. Basierend auf einem besseren Verständnis der in dieser Studie verwendeten Prozeduren und Datenanalyse schlagen wir einige alternative Erklärungen der Ergebnisse vor.

### A Critical Commentary on 'Partial Antagonism of Placebo Analgesia by Naloxone'

As part of a systematic review of studies on the mechanism of placebo analgesia [1] we read a paper by Grevert and coworkers [2, 3]. We found it a very difficult paper and spent many hours studying it. In this contribution we comment on the study's design and its results. We hope that future readers of the article save time by reading this comment in conjunction with it.

The purposes of Grevert et al's study were threefold: '(a) to determine if placebo-induced analgesia could be demonstrated using experimental ischemic arm pain; (b) to test the hypothesis that there are consistent placebo responders by repeatedly administering to the same subjects a placebo (...); and (c), the purpose we shall focus on here, 'to test the hypothesis that endogenous opioids mediate placebo-induced analgesia (...) in subjects with experimentally induced ischemic arm pain (...) [2]. The design, a partially cross-over

study, is complicated and we refer the reader to the original publication for full details, but present a slightly simplified outline in figure 1. Briefly, fourteen subjects underwent an ischemic pain procedure followed by open administration of a placebo and a hidden infusion of saline (group S, session P-S), followed by a second pain procedure. A day later this session was repeated omitting the placebo administration (session S). On the next day a session similar to session S was held, but hidden saline was replaced by hidden naloxone (session N). These three sessions were repeated after one and two weeks. Sixteen other subjects underwent the same procedure, the difference being that the administration of placebo was followed by a hidden infusion of naloxone instead of saline (group N, session P-N). Grevert et al. varied all treatment orders ( $3 \times 3 \times 2 = 18$  possibilities), which in larger trials, allows for the evaluation of treatment order effects. Figure 1 shows (week 1 of) the design, omitting the treatment order variations for clarity. The authors conclude that naloxone partially antagonizes placebo analgesia, but only in week 2



**Fig. 1.** Slightly simplified outline of the study design employed by Grevert et al. In the true study, sessions 1, 2 and 3 and sessions 4, 5 and 6 were performed 3 times. In addition, the session order was randomized between subjects but constant within subjects. Abbreviations: ipp: ischemic pain procedure; P: administration of open saline (i. e. placebo); S: administration of hidden saline; N: administration of hidden naloxone.

The time interval between the start of the first ipp and P was 10 minutes. The time interval between P and S or N was 40 minutes. The time interval between the hidden injection of either S or N and the start of the second ipp was 20 minutes.

The design can assess many effects in different ways and the authors made the choices indicated below:

- 1 minus 2: placebo effect in group S
  - 2 minus 3: naloxone effect in group S
  - 4 minus 5: placebo effect in group N
  - 5 minus 6: naloxone effect in group N
  - (1 minus 2) minus (4 minus 5): antagonistic effect of naloxone on placebo analgesia
- Other choices of analysis include (not drawn in the figure):
- 1 minus 4: antagonistic effect of naloxone on placebo analgesia (direct comparison)
  - 2 minus 6: naloxone effect (in parallel comparison)
  - 5 minus 3: naloxone effect (in parallel comparison).

and 3, not in week 1. Grevert et al. refer to this as a 'delayed appearance of naloxone blockade' over the 3 weeks, possibly as 'a result of learning'. They wrote 'During the first placebo session subjects gave the expected response (*i. e. experimental subordination or response bias*), reporting a decrease in pain, but the reinforcer, pain relief, did not occur because of the naloxone blockade' (our italics). Note that they accept the idea that the subjects may have indicated incorrect pain scores to please the investigator. They hypothesize that subjects lied about their pain perception during the first placebo session, but that this untruthful behavior was not reinforced by true pain relief (in fact, more pain may have acted as punishment, *i. e.* as negative reinforcement) and that, as a result, the lying stopped. Then, in weeks 2 and 3 the pain scores reflect the subjects' true pain. Their learning hypothesis predicts that within the 10 pain scores collected at one minute intervals (that were averaged to a single score) the first 3 to 5 scores indicate less pain than the last 3 to 5 scores as a result of (immediate) learning. Their data could be used to test this had they not been lost (personal communication by Prof. A. Goldstein).

What alternative explanations are thinkable before we accept the one on a delayed action of naloxone over three weeks, which is at odds with existing knowledge about naloxone pharmacology?

First, could naloxone alone have an effect on the pain? Grevert et al. believed that this was *not* the case, but wanted to stay on the safe side and tried to reproduce that finding in the study. Note that a clear interpretation of their study indeed requires that naloxone alone has no effect on experimental ischemic pain ((session 2 minus session 3) = (session 5 minus session 6) = 0, see fig. 1). However, their data show that, although not statistically significant, naloxone tends to cause pain in group N in weeks 2 and 3. The effect of naloxone alone in group S (session 2 minus session 3) is not shown, but stated to be similar. Instead of publishing all the raw data from group N, data of the mean naloxone effect in group S would have been more informative. The strength of the proof that the effect of naloxone alone was not different from zero may have been far less if the data from the sessions 2 and 3 had also been used to estimate the naloxone effect. Which alternative explanations remain if we assume, with the authors, that naloxone alone has no effect on the pain? Once we accept that response bias may play a role, several alternative explanations come to mind, depending on whether we assume that the magnitude of the response bias is the same in group S and group N and whether this bias is likely to be constant over the sessions in both groups or varies in a similar way in both groups over time. At any rate, the findings in the first week

are the least problematic. However, precisely in the first week clear antagonism could not be convincingly shown (antagonism of 2.7 points on a 10 cm visual analog scale,  $p = 0.33$ ).

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