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2019

Kontinen , V & Breivik , H 2019 , ' The Yaksh-model of intrathecal opioid-studies : Still exciting four decades later ' , Scandinavian journal of pain , vol. 19 , no. 1 , pp. 3-4 . https://doi.org/10.1515/sjpain-20

http://hdl.handle.net/10138/327564
https://doi.org/10.1515/sjpain-2018-2006

Editorial comment

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https://doi.org/10.1515/sjpain-2018-2006

In 1976 Tony L. Yaksh and Thomas Rudy published a one-and-half pages paper in Science entitled "Analgesia Mediated by a Direct Spinal Action of Narcotics" [1]. This article opened two very important paths in pain medicine: it was understood that opioids can act on sites in the spinal cord, which had direct clinical applications, and that spinal effects of different classes of analgesics can be studied in a simple and practical model, using awake, behaving rodents with an intrathecal catheter implanted under anesthesia.

This happened 42 years ago. It is worth to remember that opioid receptors were demonstrated to exist in nervous tissue only 3 years earlier [2], and cloned two decades later [3]. Neuraxial – spinal and epidural – administration of opioids was rapidly accepted to clinical use [4, 5]. Interestingly, the first documented case in whom morphine was administered intrathecally, with the local anesthetic cocaine, to treat pain is from 1901, see [6].

Hundreds and hundreds of studies on spinal effects of opioids and a plethora of other possible analgesics acting via different biochemical pathways have been published since the original publication in 1976 [1]. One of the advantages of direct intrathecal administration of experimental compounds is that molecules, which would not reach the spinal cord receptors (e.g. some cannot cross the blood-brain barrier, some are rapidly metabolised after oral or parenteral administration), such as small peptides can be used as research tools.

In the present issue of *Scandinavian Journal of Pain*, another report on effects of intrathecally administered opioids studied with the Yaksh-model, by the group of Tony L. Yaksh himself, is published [7]. In this paper, the potency and some adverse effects of a series of small opioid peptides (DALDA peptides: DMT-DALDA, dDALc, dDALcn, dDAL-TICP, and dDAL-TIPP) are characterised after intrathecal bolus administration in rats. Special emphasis is put into separating motor adverse effects from actual antinociceptive effects.

These peptides are hydrophilic, like morphine, which may make it possible that they could be used to produce long-lasting effect after single intrathecal bolus dose. As continuous intrathecal administration is somewhat problematic in clinical practice, especially after the adverse effects related to use of very thin spinal catheters that have led to market withdrawals, long analgesia after a single dose would be a highly desirable property of a new spinal analgesic. Obviously, before any clinical application, more research on efficacy and safety is needed.

When the rats were treated with intrathecal morphine for 5 days before administration of DMT-DALDA, the analgesic effect was not reduced [7], as it is for morphine itself as a result of development of tolerance. This "asymmetric tolerance" is interesting, as it could possibly indicate that the peptide has better intrinsic effect compared with morphine.

For the *Scandinavian Journal of Pain* this paper opens another new area: the Journal has previously published few original papers on the preclinical or basic research on pain. It is nice to begin with a contribution of top class.

Conflict of interest: The authors declare no conflict of interest.

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