Is lidocaine a key modulator of (neuro)inflammatory processes; clinical support and molecular substantiation.

Introduction

Lidocaine is a widely used amide-type local anesthetic and class 1b antiarrhythmic. In addition to its anesthetic and antiarrhythmic effects, lidocaine has important analgesic, antinociceptive, immuno-modulating, and anti-inflammatory properties ((Weinberg, 2015)(Maab et al., 2020). Especially its anti-inflammatory properties seem to underly the broad effects recently noted and ranging from reducing the cytokine storm in ARDS from Covid-19 but also Mycobacterium tuberculosis infections as well as reducing pain in cancer patients. Although still limited, clinical evidence in combination with new plausible mechanistic insights, summarized below, may explain why lidocaine has been a neglected therapeutic stance for COVID-19 and palliative cancer care.

Clinical cases

COVID-19 & Lidocaine

1. Around April 2020, in the ICU unit of the Showa University hospital in Tokyo 7 COVID-19 patients were treated with lidocaine (DCLA initiative) under the supervision of prof. T. Kotani and dr. A.Shono. 5 patients were on a ventilator and 2 patients were on EMCO, one of them being an unhealthy heavy smoker. All seven patients are well documented and have recovered! (DCLA and ICM depart. Showa University)

2. In the Netherlands from March 2020 up till now some 20 patients with COVID-19 symptoms were successfully treated off-label with lidocaine. Performing clinical trials was denied by medical ethical boards due to the lack of information about the effectiveness of lidocaine on COVID-19. Treatment at home with OTC from internet shops available lidocaine creme was the remaining option. About 20 patients (some professional healthcare workers and medical specialists involved in COVID-19 treatment) responded within hours on this off-label treatment and recovered within days uneventful. There were also no comments of long COVID-19 signs. Without any doubt we still need a good clinical trial about this topic.

Cancer pain & Lidocaine

Lidocaine has also been applied in an 'off label' setting to a variety of terminally ill patients with advanced carcinoma. Systemic inflammation originated from the primary or metastatic tumor provides the explanation for these symptoms in (advanced) cancer, thereby decreasing the quality of life in these patients. (McKenzie et al., 2019). As an example, the results for 10 patients were presented on the German Oncology Congress, November 2019 in Baden-Baden, Germany. This group of 10 patients consisted of prostate cancer (2 patients), exocrine pancreatic cancer (4 patients), colon cancer (2 patients), ovarian carcinoma (1 patient) and breast cancer (1 patient). All patients were terminal palliative without treatment options left; purpose was to improve their Quality of Life. The Sickness impact profile for disability (SIP68) was applied for these inventory data, no other measurements could be applied in this off-label treatment. In their home situation, patients received continuous subcutaneous lidocaine 1 mg/kg/hr. by pump instead of opioids.

o Before application: SIP68: 48 (range 18-68).

o After 3 days: SIP68: 33 (range 12-58), all patients were improved.

o After 7 days: SIP68: 28 (range 12- 56), all patients were improved compared to former data.

Neuroinflammation is commonly recognized to be a key factor in pain (Xanthos and Sandkühler, 2014), (Ji et al., 2019) The working mechanism is not elucidated fully at present, but lidocaine can have an important role in it as the preliminary data from the palliative study shows. It is hypothesized that lidocaine also exerts most of its effects as a P2X7 antagonist in innate immune cells.

Finally, our model seems to be supported by some recent publications on the anti-inflammatory properties of Lidocaine to help reduce both the severity of COVID-19 cases and their pain (Diaz Vera et al., 2020) (Finnerty and Buggy, 2020) (Maab et al., 2020). Also, the relevance of purinergic signaling for cancer was put forward in a review about purinergic signaling in pancreas by Ivana Novak and coworkers (Novak et al., 2020) Understanding this mechanism needs far more research than performed till now, but the

idea of having a mechanism while using a clinical available drug with great success makes it far easier.

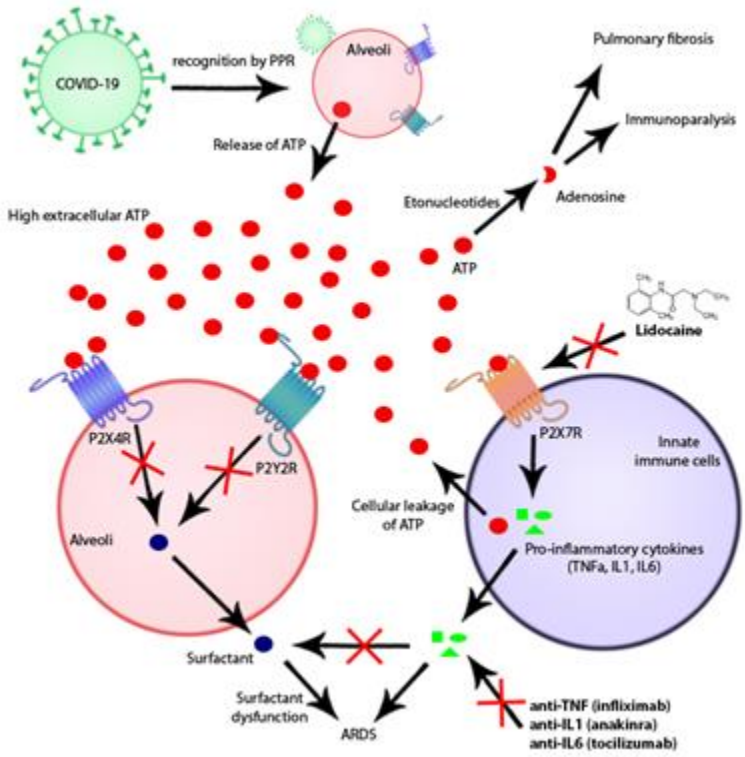
Recently these results served amongst others as a basis for the LIDOPAN study (Intravenous lidocaine for patients in pain with pancreatic cancer and chronic pancreatitis: a multicenter prospective non-randomized phase II study) with Simone Augustinus, from Marc Besselink's group at Amsterdam UMC, as study coordinator and supported by Inspire2live and the DPCG to be started in the first quarter of 2021.

New insights on lidocaine as a key modulator of (neuro)inflammation.

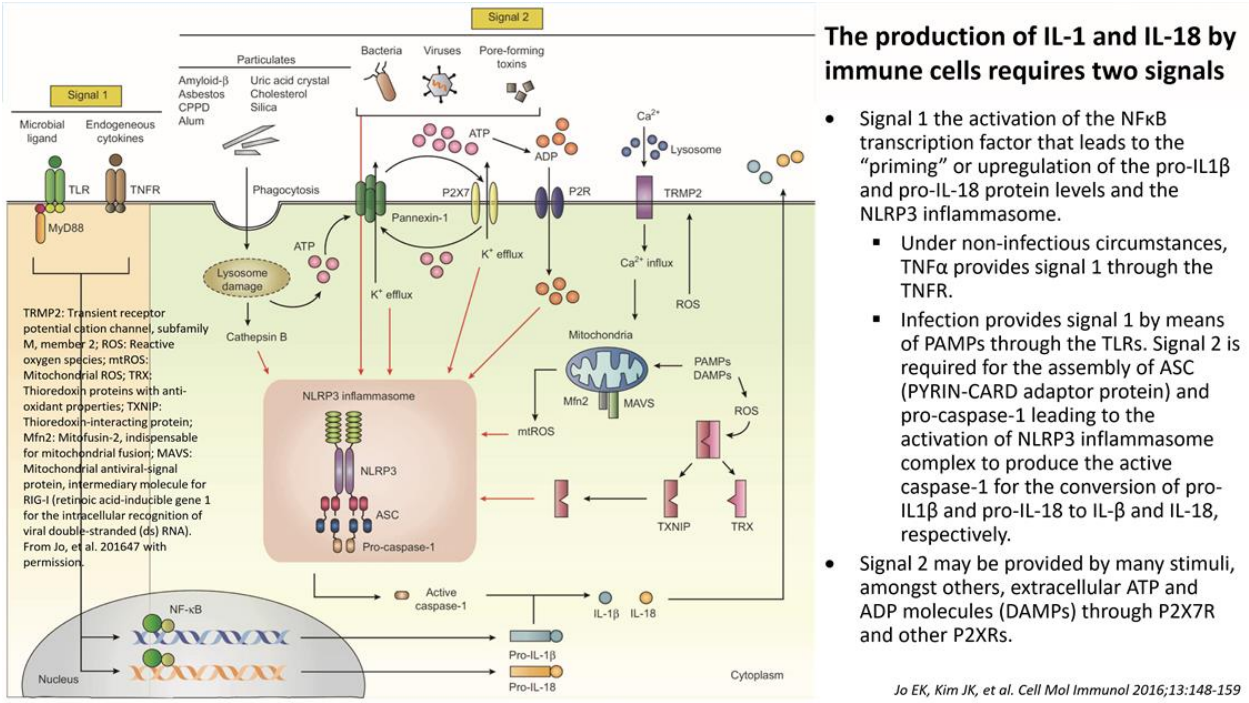
As discussed above, modulation of the (neuro)inflammatory process seems to be key for the effects of lidocaine as observed for COVID-19 as well for reducing pain with advanced cancer. In contrast to more traditional views on the underlying mechanism (Burnstock and Boeynaems, 2014) more recently it is proposed that lidocaine is a P2X7R antagonist, actually combining for the first time the biologically important disciplines of innate immunity (Wu et al., 2020)(Bodin and Burnstock) and purinergic signaling (Hasan et al., 2018). A brief molecular explanation/rationale can be summarized as follows based on COVID-19 as formulated originally by Hasan and coworkers in 2020.

The major complication of a COVID-19 infection is respiratory failure and acute respiratory distress syndrome (ARDS) (Weinberg, 2015).
Invading viral pathogens in the respiratory tract provoke cellular stress and a subsequent innate immune reaction. This causes massive exocytosis of ATP resulting in high extracellular ATP concentrations (Okura et al., 2015). Initially, this stimulates the purinergic P2Y2 and P2X4 receptors resulting in a brief period of surfactant exocytosis, however as ATP levels continue to rise, the P2X4 and P2Y2 receptors become desensitized preventing normal surfactant release. At a certain point in time, the extracellular levels of ATP exceed the lower threshold for the activation of the P2X7 extracellular ATP receptors (P2X7Rs) located on the cell surface of the innate immune cells. This triggers a pro-inflammatory response of the innate immunity followed by a massive release of inflammatory mediators and cytokine storm. The resulting vascular leakage and pulmonary edema induce the disaggregation and inactivation of pulmonary surfactant, a key element in the pathogenesis of ARDS ending in alveolar collapse and impaired gas exchange. The conversion of extracellular ATP by ectonucleotidases into adenosine activates the different adenosine receptors. This leads to secondary immune suppression, the basis of the

compensatory anti-inflammatory response syndrome (CARS) sometimes followed by pulmonary fibrosis (Wang et al., 2015). (Fig. 1)



Here we propose targeting the P2X7R in COVID-19 ARDS patients with lidocaine. Lidocaine is widely known and used as a safe analgesic drug. It inactivates fast voltage-gated Na+ channels and restricts neuron transmission (Galam et al., 2016) . However, it has also been described as a potent and selective P2X7R inhibitor (Jo et al., 2016) . Both pharmacological inhibition (Russell et al., 2020) and P2X7R knock-out (Néel et al., 2014) do increase survival in ARDS in preclinical models, thereby emphasizing one of the important functions of the NLRP3 inflammasome as visualized in Fig 2 (Conway et al., 2017)



The production of IL-1 and IL-18 by immune cells requires two signals

- Signal 1 the activation of the NFκB transcription factor that leads to the "priming" or upregulation of the pro-IL1β and pro-IL-18 protein levels and the NLRP3 inflammasome.
  - Under non-infectious circumstances, TNFα provides signal 1 through the TNFR.
  - Infection provides signal 1 by means of PAMPs through the TLRs. Signal 2 is required for the assembly of ASC (PYRIN-CARD adaptor protein) and pro-caspase-1 leading to the activation of NLRP3 inflammasome complex to produce the active caspase-1 for the conversion of pro-IL1β and pro-IL-18 to IL-β and IL-18, respectively.
- Signal 2 may be provided by many stimuli, amongst others, extracellular ATP and ADP molecules (DAMPs) through P2X7R and other P2XRs.

Jo EK, Kim JK, et al. Cell Mol Immunol 2016;13:148-159

We hypothesize that lidocaine has an anti-inflammatory effect which can be used to prevent progression into ARDS and to treat ARDS in COVID-19 patients.

The anti-nociceptive agent lidocaine has a clear advantage over other immunosuppressive drugs since it mainly targets hyperactivity of the innate immune system by inhibition of the P2X7 receptor. For example, corticosteroids result in broad immunosuppression diminishing the ability to fight the viral infection, ((Galoș et al., 2020) humanized monoclonal antibodies (i.e., tocilizumab and anakinra) are feared for their severe side effects (Fisher et al., 2000) (Bailey et al., 2018).

Safety and applications

According to literature lidocaine infusions have a strong record of safety in clinical medicine. They are frequently used in chronic pain conditions and in gastrointestinal surgery where they have been shown to reduce postoperative opioid requirements and enhance bowel recovery (Galoș et al., 2020) (Fisher et al., 2000) (Bailey et al., 2018). Most of the applications were intravenously with different doses; the higher the dose the more side effects as know from the general description by the EMA (European Medicines Agency) on lidocaine.

This more or less standard application is intravenous infusion but also due to its hypothesized working m8echanism as described, subcutaneous infusion seems more effective and longer lasting by an unknown mechanism, but clinical effects are seen with even lower dosage than 1/mg/kg/hour. This pharmacological distribution and its clinical effects must certainly become subject of more research. As in seen in pain care an individual treatment will be necessary. The preliminary effects noticed in a very small group till now, are however impressive.

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