Quantifying nociception could clarify the sites of action of analgesics. For example, in the field of thoracic analgesia, there has been debate about interpleural local anaesthetics. Whether action is by diffusion to intercostal nerves or on pleural sites that also feed nociception along the phrenic and vagus nerves could be demonstrated with a disaggregation methodology.

And it is not only local anaesthetic pharmacodynamics to which pain disaggregation theory could be applied. The observation that the fentanyl group were discomforted more by arm movement than coughing, in comparison to those who had intercostal nerve block or systemic opioid, is probably a reflection of the small numbers in the former and not repeatable. But it may have other significance. That fentanyl suppresses the cough reflex can be discounted. The cough manoeuvre was contrived for the studies and is not a natural observation. A distant possibility is that the dynamic pain scoring technique has shown a marker for a segmental action of opioids such as fentanyl. Also, a new problem is emerging in clinical practice ± that of acute tolerance to opioids following the intraoperative use of remifentanil. The descriptions of the pain experiences of some of these patients are new and there is anecdotal evidence of disaggregation phenomena to such an extent that old operations are requiring the application of novel multimodal analgesic regimens.

Applying the logic that follows from a theory based on quantum nociception extends to clarification of the activity of a third component of multimodal regimens: the non-steroidal anti-inflammatory drugs. Current belief is that these drugs reduce a ‘nocigenic soup’ of inflammatory mediators. This may be a quantifiable reduction measurable with double-blind, placebo-controlled methodology. The effect and influence of pre-emptive techniques on post-operative pain could similarly be measured. Therefore, it is to be hoped that, besides enlightening the science of clinical analgesia, a paradigm of quantum nociception ultimately will lead to improvements in patient care.

References
skeletal muscle, result from central serotonergic overstimulation or from a porcine stress syndrome remains unresolved. In this study the in vivo effects of DOI on anaesthetized (and thus stress-protected) MHS and MH-normal (MHN) pigs were investigated.

**Methods and results.** DOI 1 mg kg⁻¹ was administered three times at 40-min intervals to five MHS and five MHN anaesthetized pigs. Body temperature, heart rate, muscle tone, arterial carbon dioxide pressure (\(P_{aCO_2}\)), pH and creatine kinase concentrations were measured. The clinical occurrence of MH was defined by \(P_{aCO_2}\) above 70 mm Hg and an increase in body temperature of more than 2 °C. Intragroup differences were analysed with the Friedman test as an overall non-parametric ANOVA and, in case of significance, with the Wilcoxon test. Intergroup comparisons were performed with the Mann–Whitney U-test (statistical significance \(P<0.05\)). MHS and MHN pigs developed muscle fasciculations, significant increases in body temperature and \(P_{aCO_2}\) and a significant decrease in pH after the administration of DOI. These changes were comparable in both groups until the third dose of DOI, when in MHS pigs heart rate and \(P_{aCO_2}\) rose significantly and pH fell significantly compared with MHN pigs. All MHS pigs fulfilled the MH criteria. Body temperature increased by more than 2 °C in all MHN pigs and \(P_{aCO_2}\) exceeded 70 mm Hg in two. Thus, two MHN pigs fulfilled the criteria of MH.

**Conclusions.** The comparability of the clinical presentation following DOI administration in MHS and MHN animals and the order of the development of MH-like symptoms favour the hypothesis of a central serotonergic overstimulation, leading to a serotonin syndrome.

**Keywords:** agonists serotonergic, DOI; anaesthetics volatile, halothane; analeptics, caffeine; complications, malignant hyperthermia; complications, serotonin syndrome

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analysis was performed with the non-parametric Mann–Whitney U-test. P<0.05 indicated statistical significance.

The median body temperature in MHS pigs before the first dose of DOI was 36.6 (range 35.8–38.5) °C. The temperature increased to 37.7 (36.9–39.6) °C 40 min after the first dose of DOI, 38.9 (38.3–42.1) °C 40 min after the second dose and 41.5 (39.6–42.8) °C 40 min after the last dose. MHN animals had a baseline body temperature of 37.8 (35.7–39.1) °C. The temperature increased to 38.7 (37.5–39.7) °C 40 min after the first dose of DOI, 39.6 (37.6–40.7) °C 40 min after the second dose and 40.3 (38.1–41.5) °C 40 min after the last dose. Statistical analysis showed a significant temperature increase in the MHS and MHN groups, but no significant intergroup variations.

P\textsubscript{aCO2} increased significantly in both groups (Fig. 1) but there was a significant difference between the two groups only after the third dose of DOI.

The first dose of DOI induced a significant decrease in pH from 7.46 (7.42–7.47) to 7.30 (7.26–7.38) in the MHS group. The second dose decreased pH to 7.24 (7.05–7.32) and the third to 7.13 (6.84–7.17). The pH values decreased significantly after the first dose in the MHN pigs from 7.49 (7.41–7.56) to 7.35 (7.31–7.44), but remained virtually unchanged for the rest of the experiment. The intergroup comparisons showed a significant difference in pH after 120 min only.

In the MHS pigs, heart rate rose significantly from the baseline value of 60 (55–94) beats min\(^{-1}\) to 66 (61–91) beats min\(^{-1}\) after the first DOI dose, 85 (65–205) beats min\(^{-1}\) after the second dose and 115 (87–174) beats min\(^{-1}\) after the third dose. In contrast, no significant changes in heart rate occurred in MHN pigs. After 120 min, however, a significant difference in heart rate was found between the groups.

Non-significant but higher baseline creatine kinase concentrations were measured in MHS pigs (median 7.7 u litre\(^{-1}\), range 5.5–18.9 u litre\(^{-1}\)) compared with MHN pigs (4.8 u litre\(^{-1}\), 4.2–8.1 u litre\(^{-1}\)). In both groups, the cumulative challenge of DOI exerted only slight effects on creatine kinase activity. Both MHS and MHN pigs developed skeletal muscle fasciculations. Muscle rigidity was not observed, however.

All MHS pigs fulfilled the MH criteria during the experiment. Body temperature increased by more than 2 °C in all MHN pigs and P\textsubscript{aCO2} exceeded 70 mm Hg in two MHN animals. Thus, two MHN pigs fulfilled the criteria of MH.

**Comment**

Lösch and colleagues\(^5\) studied the *in vivo* effects of the 5HT\(_{2A}\) receptor agonist DOI in conscious MHS pigs. In addition to altered behaviour, typical MH signs such as muscle rigidity and hyperthermia and metabolic changes such as elevated P\textsubscript{aCO2}, lactate and creatinine kinase concentrations and lowered pH were observed in MHS but not in MHN pigs. Thus, DOI was interpreted as an MH triggering agent. Three underlying pathways may be responsible for the MH-like signs and symptoms after the administration of 5HT\(_{2A}\) agonists in conscious pigs. Firstly, direct substance-specific effects on peripheral sites, such as an activation of the skeletal muscle cell via 5HT\(_{2A}\) receptors resulting in an MH crisis could be responsible. A typical fulminant MH crisis is characterized by generalized fasciculations in MHS pigs.\(^6\)–\(^8\) Five min after the administration of trigger agents, hypercapnia, hypoxaemia, increased lactate concentrations and lowered pH are found. Cardiovascular responses include initial hypotension, tachycardia, increased cardiac output and arrhythmias. As a late sign of MH, a significant increase in body temperature is not found until 10 min after exposure to a trigger substance.\(^8\) Secondly, a porcine stress syndrome could be responsible. This syndrome describes MHS animals which are adversely affected by stress induced by trucking, fighting, coitus and crowding.\(^5\) In this context, the hallucinogen-induced psychosis in conscious pigs might lead to a central stress induction, which secondarily results in the MH-like changes in skeletal muscle metabolism. The third hypothesis emphasizes a 5HT\(_{2A}\)-specific central agonist action, like the serotonin syndrome.\(^10\)

Our *in vivo* experiments did not show an unequivocal difference in the defined MH criteria in the study groups.
Fasciculations and comparable increases in temperature, $P_{aCO_2}$, and a decline in pH were monitored after the first and second challenge of DOI in both groups of pigs. However, differences in heart rate, pH and $P_{aCO_2}$ between MHS and MHN did not occur until the third dose of DOI.

The predictive value of our study may be reduced because the two groups of pigs had significantly different weights. (There was no difference in age.) The weight difference could possibly explain the lower resting temperature in MHS compared with MHN pigs. In addition, a lower body temperature might be an MH-protective factor in pigs.

The results of the present study are in contrast to the typical course of MH in susceptible swine. Furthermore, the well-known trigger substances cannot induce MH in normal animals. It is notable that Löscher and colleagues described MH crises in conscious pigs at a lower concentration of DOI (0.8 mg kg$^{-1}$). Thus, it is tempting to speculate that different mechanisms are responsible for the induction of MH by 5HT$_{2A}$ agonists and known MH trigger agents. The prolonged onset of clinical signs and symptoms, with similarity in the course of temperature, $P_{aCO_2}$, and pH in the two groups of pigs is in accordance with a serotonin syndrome. Consequently, DOI does not seem to be a direct MH triggering agent in vivo in swine. However, 5HT$_{2A}$ receptor agonists might secondarily trigger a porcine stress syndrome in conscious swine by inducing central psychotic alterations, which could be prevented by anaesthesia.

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