

Nitrous Oxide Interacts with Opioid Receptors: More Evidence

To the Editor:—The paper by Ngai and Finck¹ provides convincing further evidence of interaction of nitrous oxide (N₂O) at analgesic concentrations on the endorphinergic system.

However, we cannot agree with these authors in regard to their suggestion that the interaction is not a receptor interaction, but rather secondary to the release of endogenous opioid substances.¹ We have hypothesized that N₂O interacts with the opioid receptors.² This idea is supported by much evidence. Ahmed and Byrne have shown that ³(H) dihydromorphine is displaced from binding sites by analgesic concentrations of N₂O.³ The analgesic effect of ketamine has been shown to be mediated by opioid receptors.⁴ Lower doses of this agent are required when used in humans if combined with analgesic concentrations of N₂O.⁵ This could indicate that N₂O and ketamine act synergistically at the opioid receptor to cause this effect.*

Moreover, Maruyama *et al.* have shown that the combined effect of morphine and N₂O was less than that of morphine alone.⁶ This indicated to us that N₂O interfered with the receptor occupation of morphine.⁷ In terms of molecular pharmacology these findings are consistent with a model of competitive dualism.⁸ The inference from this is that N₂O may well function as a partial agonist at the opioid receptor.

The finding that CSF levels of beta endorphin are not raised⁹ by analgesic concentrations of N₂O (70%) during anesthesia is telling evidence in favor of our view.

Thomas *et al.* also have suggested since systemic blood levels of beta endorphin are raised to a greater extent by Etonox (50% N₂O + 50% O₂) than by pethidine during labor,¹⁰ that N₂O causes its analgesic effect by indirect means, *viz.* release of endorphins. However, it has been shown that catecholamines are potent stimulators of beta-endorphin release into the systemic circulation.^{11,12} In addition, it is known that N₂O administration can cause a rise in catecholamine levels in the systemic circulation,¹³ which is not the case for pethidine.¹⁴ It is therefore conceivable that these differences observed by Thomas *et al.* are related to this factor. Furthermore, CSF levels are a much more accurate

measure of neurotransmitter changes in the CNS than are changes in blood level of these substances.

Ngai and Finck¹ note that, as in the cases of other workers,¹⁵ isolated organ bath experiments have not demonstrated a receptor interaction of N₂O on gut contractions. We (Dreyer and Gillman: unpublished observations) also have failed to demonstrate such changes, but this appeared to be due to technical difficulties inasmuch as the presence of N₂O tended to cause the preparation to become totally unresponsive to all stimuli. Negative findings *per se* do not rule out a receptor interaction since Paton has demonstrated that a rapid acute tolerance occurs to the effects of morphine¹⁶ if it is left in contact with the preparation for more than 3 min. It is difficult to visualize a method of obtaining adequate concentrations of N₂O in an organ bath within 3 min. Furthermore, Cox and Weinstock,¹⁷ have shown that in 15% of guinea pigs ileal preparations that morphine was without effect. These factors emphasize the obvious difficulties associated with using a gas *in vitro*, and would suggest that positive findings are of greater significance than negative ones.

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REFERENCES

1. Ngai SH, Finck AD: Prolonged exposure to nitrous oxide decreases opiate receptor density in rat brainstem. *ANESTHESIOLOGY*, 57:26-30, 1982
2. Gillman MA, Lichtigfeld FJ: A comparison of the effects of morphine sulfate and nitrous oxide analgesia on chronic pain states in man. *J Neurol Sci* 49:41-45, 1981
3. Ahmed MS, Byrne WL: Opiate receptor binding studies influence of a reversible sulfhydryl reagent, Endogenous Opiate Agonists and Antagonists. Edited by Way, EL. New York, Pergamon, 1980, pp 51-54
4. Finck AD, Ngai SH: Opiate receptor mediation of ketamine analgesia. *ANESTHESIOLOGY* 56:291-297, 1982

* Gillman MA: Is nitrous oxide an opiate agonist? Dissertation accepted in partial fulfillment of requirements for degree of M.Sc. at Potchefstroom University for C.H.O., South Africa, 1981.

5. Wessels JV, Gary MC, Allen W, et al: The effect of nitrous oxide on ketamine anesthesia. *ANESTHESIOLOGY* 39:382-386, 1973
6. Maruyama Y, Shimoji K, Shimizu H, et al: Effects of morphine on human spinal cord and peripheral nervous activities. *Pain* 8:63-73, 1980
7. Gillman MA, Lichtigfeld FJ: The similarity of the action of nitrous oxide and morphine *pain* 10:110, 1981
8. Ariens ES, Simonis AM, Van Rossum J, et al: Receptor interactions Section 11A, *Molecular Pharmacology* vol 1. Edited by Ariens EJ. New York, Academic Press, 1964, pp 119-269
9. Way WL, Hosobuchi Y, Eger EI, et al: Anesthesia does not increase cerebrospinal fluid opioid peptides in humans. *Anesth Analg (Cleve)* 61:223, 1982
10. Thomas TA, Fletcher JE, Hill RG: Influence of medication pain and progress in labour on plasma B-endorphinlike immunoreactivity. *Br J Anaesth* 54:401-408, 1982
11. Berkenbosch F, Vermes I, Tilders FJH: Epinephrine as a potent releaser of immunoreactive B-endorphin in rats. *Eur J Pharmacol* 72:97-100, 1981
12. Cohen MR, Pickar D, Dubois M, et al: Stress-induced plasma beta-endorphin immunoreactivity may predict postoperative morphine usage. *Psychiatry Res* 6:7-12, 1982
13. Marshall B, Wollman H: *General anesthetics, The Pharmacological Basis of Therapeutics*, 6th edition. Edited by Gilman AG, Goodman LS, Gilman A. New York, Macmillan Publishing Co. Inc., 1980, pp 276-299
14. Joffe JH, Martin WR: *Opiate analgesics and antagonists, The Pharmacological Basis of Therapeutics*, 6th edition. Edited by Gilman AG, Goodman LS, Gilman A. New York Macmillan Publishing Co. Inc., 1980, pp 494-534
15. Lawrence D, Livingston A: Opiate-like analgesic activity in general anesthetics. *Br J Pharmacol* 73:435-422, 1981
16. Paton WDM: The action of morphine and related substances on contraction and on acetylcholine output of coxially stimulated guinea-pig ileum. *Br J Pharmacol* 11:119-127, 1957
17. Cox BM, Weinstock M: The effect of analgesic drugs on the release of acetylcholine from electrically stimulated guinea-pig ileum. *Br J Pharmacol Chemother* 27:81-92, 1966

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Pulmonary Vascular Impedance: Resistance *versus* Pulmonary Artery Diastolic-Pulmonary Artery Occluded Pressure Gradient

To the Editor:—The article, "Pulmonary Vascular Responses to Nitrous Oxide in Patients With Normal and High Pulmonary Vascular Resistance," by Drs. Schulte-Sasse, Hess, and Tarnow¹ introduces the question of which hemodynamic parameter best reflects drug-produced changes in impedance in the pulmonary circulation. In many hemodynamic studies (including this article), this question is answered by calculating pulmonary vascular resistance (PVR)

$$\text{PVR (dyn} \cdot \text{s} \cdot \text{cm}^{-5}) = \frac{\text{PAP} - \text{PAo}}{\text{CO}} \times 80 \quad (\text{Eq. 1})$$

However, this calculation may be inappropriate and misleading in certain circumstances. For example, mean pulmonary artery pressure (PAP) and calculated PVR are influenced by both passive (flow, left heart filling pressure) and active (chemical, neurogenic) factors. The administration of a drug (*e.g.*, nitrous oxide) may decrease CO (negative inotropic effect) and increase PAP (active vasoconstriction). The effect of these changes would be to increase calculated PVR. However, the cardiac depression resulting from nitrous oxide inhalation may increase pulmonary artery occluded pressure (PAo) and decrease calculated PVR. The overall impact of these opposing responses on the passive and active factors may make conclusions based on changes in calculated PVR difficult to interpret. Furthermore, the equation for PVR is based on the principle of Ohmic resis-

tance which states that resistance is related to the pressure drop across the vascular bed divided by the flow (Poiseuille's law). However, the validity of this relationship in the pulmonary circulation assumes blood flow is continuous throughout the cardiac cycle and the pulmonary vessels are sufficiently rigid that pressure generated within them results from flow rather than volume.² This assumption is more likely to be valid in hydraulic systems with rigid walls than in the compliant pulmonary vascular bed. In fact, the resistance vessels (muscular arteries) in the pulmonary circulation are so highly compliant that pulmonary blood flow and PVR are negligible at the end of cardiac diastole.² This explains the observation that in the absence of increased PVR (impedance), no significant gradient exists between pulmonary artery end-diastolic pressure (PADP) and PAo. Indeed, this pressure gradient (PADP-PAo) has been suggested as a better measure of obstruction to flow in the pulmonary circulation compared with calculated PVR.² The advantage of this pressure gradient compared with calculated PVR is demonstrated in the data of Harvey and Enson.² These authors compared PVR values and (PADP-PAo) gradients in several groups of patients with mitral stenosis and severe pulmonary hypertension. They observed significant changes (100%) in calculated PVR values between patient groups despite the absence of changes in the measurement of PAP, PAo, PADP, and (PADP-PAo) gradients in each