Differentiation of Two Types of Pain by Anesthetics

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The pain thresholds, to a cutaneous thermal stimulus and to a tibial pressure stimulus were measured before, during, and after the administration of nitrous oxide (25–30 per cent in oxygen), halothane (0.5 per cent) and sodium thiopental (100–150 mg. in 10 minutes). The thermal pain and the tibial pressure pain thresholds rose with nitrous oxide and halothane. The thermal pain threshold rose with sodium thiopental but simultaneously the tibial pressure pain threshold fell. It is deduced that the sensations produced by these two stimuli are neurologically different and that the known differences between the actions of barbiturates and inhalational anesthetic drugs on presynaptic inhibition in the spinal cord can account for this differentiation.

THE OBSERVATION that the threshold of pain elicited by tibial pressure was lowered by small doses of barbiturates was made by Clutton-Brock.[1] The term *antanalgesia* or *anti-analgesia* was applied to this phenomenon. Thus we find that, as a result of pain threshold studies of this sort that nitrous oxide, trichlorethylene, cyclopropane and ether are classed as analgesic drugs whereas halothane, sodium pentobarbital, sodium phenobarbital and sodium thiopental have anti-analgesic properties.[2, 3] Some observations have been made on unconscious subjects and the results have been based on flexion reflex activity in response to tibial pressure.[4] This, however, only provided evidence of depression of multisynaptic cord reflex pathways and cannot be accepted as evidence of analgesic property.

Clutton-Brock[5] attributed anti-analgesia to the inhibition of an ascending, reticulo-cortical inhibitory system, thereby causing facilitation of transmission or perception of pain. The U-shaped curve of effect of sodium thiopental on the tibial pressure pain threshold was equated with the effects of the barbiturates on this ascending inhibitory system.[6]

The clinical study of pain is extremely complex. Pain depends upon many factors: site, type and intensity of stimulus, presence or absence of simultaneous stimuli of other modalities of sensation, psychological factors such as past experience, attention, distraction, anxiety and the emotional content of the environment, to mention but a few.[7] The results obtained with objective studies of threshold effects of drugs do not always agree with the effects of such drugs in the presence of natural pain.

Cutaneous sensation has been looked upon as being entirely due to stimulation of specific receptors, the information being carried to the central nervous system by modality specific nerve fibers.[8] This theory implies that sensation is differentiated entirely at the receptor level and that processes of temporal and spatial summation and inhibition within the central nervous system, apart from cognitive processes are not concerned with interpretation of sensation. It now seems to be clear that in whatever form the information arising in peripheral receptors reaches the central nervous system it is profoundly modified by presynaptic inhibition at the primary afferent terminal arborization, by the response characteristics of neurons in the central nervous system in relation to their properties of threshold, adaptation and temporal summation of activity, and by the afferent traffic in other parts of the central nervous system.[9]

A vast amount of experimental work has been carried out to establish central pathways for sensation and it has been concluded that information related to specific sensory modalities travels by fairly well defined pathways in the spinal cord and brainstem. Thus Rose and Mountcastle[10] state that sensations of pain, temperature and tickle depend upon the integrity of spinothalamic systems. Touch

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and kinesthesis are concerned with the medial lemniscal system as is sensation from periosteum, fascia and tendon sheath. Some fibers related to touch travel in the anterolateral system. Pain, however, may not ascend in the cord in the spino-thalamic system exclusively, and Sweet [11] quotes the relevant evidence from human experiment and clinical experience. In view of the discussion by Melzack and Wall [9] it might be more proper to say that patterns of nerve impulses which the brain recognizes as belonging to painful stimuli would appear to depend on the integrity of the anterolateral system for their transmission or formation, or that, without the activity which customarily reaches the central nervous system by the anterolateral tracts pain cannot be appreciated in the normal way. The term *pain-tract* can be considered as a misleading oversimplification, but is so termed because its section frequently abolishes pain.

Pain, whether it arises from certain patterns of impulses reaching the central nervous system as a result of stimulation of "specific receptors" or of "pain fibers," is thought of as one modality of sensation although it is recognized to have qualities which differ with its origin and with the type of stimulus.

Beecher and others [7, 12] have reported that barbiturates are capable of relieving pain in some circumstances, although the work referred to by Clutton-Brock [3] implied that in light doses it increased pain. These reports and the evidence presented in this introduction led us to compare the effects of some of the anesthetic drugs upon pain of two clinical qualities. It appeared to us that since barbiturates exert effects in the central nervous system which differ from those exerted by other drugs (see discussion) that pain of differing subjective descriptions might possibly be differentiated by them.

Methods

Experiments were carried out on healthy volunteers, either medical students, hospital anesthesia residents or medical anesthesia staff. They were held in a quiet, air-conditioned room with a minimum amount of general noise, interruption or disturbance. The subjects lay on a comfortable trolley and while relaxing had the procedure explained in full. An effort was made to quell any anxiety which they may have had.

In all experiments oxygen was administered for ten minutes before control testing began, the anesthetic was given for ten minutes, and observations were made and this was followed by a waiting period of ten minutes on oxygen alone before the final control observations were made.

Nitrous oxide concentration was controlled by flowmeters, halothane was vaporized with a Fluotec vaporizer and its concentration controlled by frequent estimations made with a calibrated ultraviolet halothane analyzer. Sodium thiopental was administered in 1 per cent solution by means of a motor driven syringe (Harvard Apparatus Co.) and delivered into a side arm of a 5 per cent dextrose drip which was set up in the arm of the subjects. Scalp-vein needles (Abbott No. 23) were used so that comfort and mobility of the arm was achieved.

The method of estimation of the superficial pain threshold has been described in full.[13] In brief, a fine platinum wire, wound round a U-shaped glass rod so that one half turn traversed the bend of the U, was pressed on either thenar eminence sufficiently firmly to occlude capillary blood flow. The wire was heated with a current provided by a Variac variable transformer supplying the primary winding of a vacuum tube filament (6.3 v.) transformer. The voltage thus varied from zero to 6.3 volts and was supplied to the platinum wire. During testing the primary voltage was increased slowly but at a constant rate until the cold wire became warm and then hot enough to produce pain. At this point the subject removed it and the voltage reading of the Variac was recorded as the threshold in volts. It is realized that expressing the threshold in volts is not quantitative because the energy supplied to the skin cannot be estimated, but we were interested in comparative readings only. The hands were alternated after each estimate.

The threshold of pain produced by tibial pressure was estimated by the method described by Clutton-Brock.[3] The pan of a spring balance (Salter 0–20 pounds) was replaced by a flat-headed screw of 9.5 mm. diameter, padded with adhesive tape. The screw

TABLE 1. Pain Threshold Effects of 25–30 Per Cent Nitrous Oxide in Oxygen

Subject	Thermal Stimulus (Volts) Mean ± Standard Error			Tibial Pressure (Pounds Pressure) Mean ± Standard Error		
	Control	Drug	P	Control	Drug	P
1	38.0 ±0.46 (20)	45.9 ±2.08 (10)	0.001	6.92±0.43 (10)	13.18±1.36 (5)	0.001
2	47.74±0.48 (23)	53.89±0.74 (9)	0.001	7.5 +0.62 (11)	16.6 +3.09 (6)	0.001
3	30.5 ±0.60 (20)	31.7 ±0.52 (10)	0.2–0.3	12.08±0.63 (11)	11.5 ±1.79 (6)	0.35
4	40.25±0.41 (24)	43.7 ±0.42 (10)	0.001	12.86±0.42 (10)	19.9 ±1.08 (5)	0.001
5	36.7 ±0.44 (21)	42.2 ±1.0 (10)	0.001	5.78±0.24 (12)	11.0 ±0.47 (6)	0.001
6	41.25±0.59 (20)	46.8 ±0.88 (10)	0.001	15.33±0.81 (10)	19.6 ±0.29 (5)	0.005–0.001
7	67.06±0.49 (31)	72.0 ±0.63 (10)	0.001	8.6 ±0.39 (10)	10.06±0.89 (8)	0.05–0.01
	Mean change = 11.5 per cent rise			Mean change = 52.5 per cent rise		

( ) = Number of observations.

was pressed with slowly increasing force on the middle third of the antero-medial surface of the tibia, the angle of application being normal to the surface. The pressure in pounds required to produce pain was recorded as the threshold. Each area was marked and not reused and alternate legs were used for successive estimations.

The order of testing was varied from subject to subject, and five subjects with sodium thiopental had alternate measurements with heat and with pressure in each run. Sodium thiopental was given at a rate of 15 mg./minute to a total dose of 100 to 150 mg. and testing was carried out subsequently. This dosage of sodium thiopental was selected because it had little subjective effect on most subjects; and although thresholds were recorded as control observations after a ten-minute waiting period, full recovery to initial values took longer in some subjects.

Nitrous oxide 25–30 per cent was arbitrarily used and it was not intended to equate its analgesic effects with those of other drugs. Similarly 0.5 per cent halothane was selected.

The grouped control results and the results obtained under anesthesia were tested for the significance of difference between their means by Student's *t* test. The probability *P* refers to the probability that the observed differences could have arisen by chance alone.

Results

Nitrous Oxide. Seven subjects had both thresholds tested, the results being presented in table 1. Subject 3 was little affected by this concentration of nitrous oxide, showing no significant change in either of the thresholds. All the other subjects showed a significant rise in the thermal pain threshold. All subjects except 3 showed a significant rise in the tibial pressure threshold.

TABLE 2. Pain Threshold Effects of 0.5 Per Cent Halothane

Subject	Thermal Stimulus (Volts) Mean ± Standard Error			Tibial Pressure (Pounds Pressure) Mean ± Standard Error		
	Control	Drug	P	Control	Drug	P
2	44.6 ±0.35 (20)	48.83±1.30 (6)	0.001	13.57±0.37 (12)	19.29±0.63 (6)	0.001
5	42.96±0.64 (25)	43.0 ±1.47 (11)	1.0	5.78±0.65 (12)	9.48±0.46 (6)	0.01
8	42.52±0.39 (27)	45.05±0.88 (20)	0.001	8.17±0.45 (12)	9.03±0.43 (6)	0.1–0.15
9	77.19±1.0 (21)	81.7 ±0.82 (10)	0.005	9.61±0.50 (11)	11.91±0.54 (6)	0.005–0.01
10	75.19±0.69 (31)	79.23±2.05 (10)	0.005	14.55±0.78 (12)	18.64±0.66 (5)	0.01–0.025
	Mean change = 6.6 per cent rise			Mean change = 33 per cent rise		

( ) = Number of observations.

TABLE 3. Thermal Pain Threshold Effect of 0.15–0.25 Per Cent Halothane

(Volts–Mean ± Standard Error)

Subject	Control (25–30% N_2O) (After 10 Minutes of 25–30% N_2O)	Addition of 0.15–0.25% Halothane for 10 Minutes	P
13	63.10±1.23 (10)	68.00±1.29 (10)	0.005–0.01
14	78.80±1.18 (10)	88.25±1.85 (10)	0.001
9	65.90±1.96 (10)	71.35±0.94 (10)	0.005–0.01
10	71.60±1.73 (10)	81.20±2.53 (10)	0.001
15	70.05±0.76 (10)	74.90±1.74 (10)	0.01–0.025
	Mean change = 9.6 per cent rise		

( ) = Number of observations.

Halothane. All subjects except 5 showed a significant rise in the threshold of pain elicited by heat. The tibial pressure threshold rose in all subjects but significantly in only four of the five tested. The results are presented in table 2.

To test the reported anti-analgesic effect of halothane, five subjects were given 25 per cent nitrous oxide during the control period and after measuring the thermal threshold, 0.15 per cent to 0.25 per cent halothane was added for ten minutes and the threshold again measured. In each subject this quantity of halothane significantly enhanced the analgesic effect of nitrous oxide. Table 3 presents the results.

Sodium Thiopental. The data are presented in table 4. The threshold elicited by heat was significantly raised by the drug in all but two of the ten subjects tested. The tibial pressure pain threshold was reduced in all subjects although significantly in only five.

The actual recorded voltages cannot be compared in any subjects because two thermal stimulators were used, the wires differing slightly in resistance.

Discussion

The results show that nitrous oxide and halothane cause a rise in the thermal pain threshold and the threshold of pain elicited by tibial pressure. No diminution of the thermal pain threshold could be demonstrated with the administration of halothane when the threshold was elevated with nitrous oxide.

Sodium thiopental raised the thermal pain threshold and simultaneously diminished the tibial pressure pain threshold. Considerable confirmation for the reduction of tibial pressure pain threshold exists in the literature with similar dosage to that used in these experiments.[3]

Thus we have demonstrated that the three drugs tested are analgesics in the accepted sense of dulling the appreciation of pain in concentrations which do not overtly impair consciousness. Halothane was used in 0.5 per cent concentration because no consistent elevations of thresholds could be detected with less. At this concentration most subjects appeared to be closer to unconsciousness than they appeared to be with sodium thiopental given at 15 mg. per minute or with 25–30 per cent of nitrous oxide.

The phenomenon of a rise in the threshold to thermal pain with a simultaneous fall in that due to tibial pressure with the administration of low doses of sodium thiopental requires some explanation.

We did not determine the point at which the tibial pressure pain threshold became elevated since it was sufficient for our purpose to demonstrate this difference. The two methods used to elicit pain are not particularly important and we would not like to hazard a guess as to the types of receptor or receptors, or even as to the exact location of the receptors which were being stimulated to cause pain in each case. The results indicate that whatever information travels within the central nervous system as a result of each stimulus, one differs from the other. Experimental observations by Eccles and his colleagues[14] showed that pentobarbital and thiamylal markedly increase the extent and duration of presynaptic inhibition on all types of large primary afferent terminals entering the spinal cord. Since pathways mediating presynaptic inhibition have at least two synapses, large doses of barbiturates depress presynaptic inhibition by depressing interneuronal conduction in this pathway. Moreover, it is known that descending pathways from the cortex and brainstem act on primary afferent terminal arborization by presynaptic inhibition and that the process is also important at all arborizations

TABLE 4. Pain Threshold Effects of Sodium Thiopental (100–150 Mg. in 10 Minutes)

Subject	Thermal Stimulus (Volts) Mean ± Standard Error			Tibial Pressure (Pounds Pressure) Mean ± Standard Error		
	Control	Drug	P	Control	Drug	P
1	46.95±0.40 (20)	53.20±0.55 (10)	0.001	5.87±0.61 (15)	4.7 ±0.32 (5)	0.1–0.2
4	45.9 ±0.48 (20)	48.88±0.70 (27)	0.001	7.07±0.28 (11)	6.91±0.30 (11)	0.9
7	64.85±0.53 (20)	69.40±1.06 (10)	0.001	9.16±0.17 (11)	6.50±0.39 (5)	0.001
3	65.62±0.47 (21)	69.40±0.57 (10)	0.001	12.43±0.56 (11)	9.74±0.60 (5)	0.005
6	51.14±0.42 (21)	55.40±0.65 (10)	0.001	10.18±0.42 (11)	10.01±11 (6)	0.35–0.4
11	63.6 ±1.16 (20)	69.6 ±0.70 (10)	0.001	19.34±0.63 (20)	16.49±0.83 (10)	0.001–0.01
12	68.28±0.54 (21)	73.27±0.76 (11)	0.001	10.08±1.08 (10)	7.18±0.75 (8)	0.02–0.05
16	42.35±0.56 (20)	41.9 ±0.75 (12)	0.5	10.74±0.39 (22)	9.38±0.84 (12)	0.25–0.5
17	49.95±0.87 (20)	51.5 ±1.08 (20)	0.25–0.5	7.64±0.42 (20)	5.85±0.44 (20)	0.001
18	54.35±1.20 (20)	57.8 ±1.28 (16)	0.001	10.74±0.53 (10)	9.52±0.34 (10)	0.05–0.1
	Mean change = 6.7 per cent rise			Mean change = 16.6 per cent fall		

( ) = Number of observations.

in the afferent pathways apart from the primary arborization.[15] Ether on the other hand only depresses presynaptic inhibition by its property of depression of interneuronal conduction. It is more than probable that sodium thiopental acts similarly to pentobarbital and thiamylal and it is also likely that nitrous oxide and halothane are not dissimilar from ether in their central actions.

We, therefore, have evidence of two distinct modes of action of anesthetic drugs within the central nervous system which might afford an explanation for the observed phenomena.

The results would appear to indicate that tibial pressure pain becomes less secure in its transmission when interneuronal depression and reduction in presynaptic inhibition occur and it becomes more secure in its transmission when presynaptic inhibition is increased. Thermal pain transmission on the other hand does not appear to be influenced in the same way by presynaptic inhibition since both groups of drugs decrease security of its transmission. It is apparent, however, that whatever the physiological explanation, the central nervous system processes these two painful stimuli as different modalities of sensation.

Conclusion. It is quite clear, from the evidence presented, that pain elicited by tibial pressure differs from pain elicited by heat applied superficially to the skin in the neurological sense. These two methods of stimulation have been shown to be physiologically different by means of two types of anesthetic drug which have known differences in their actions on presynaptic inhibition at primary afferent terminal arborizations and other axo-axonal synapses.

Summary

Experiments were carried out on volunteers to examine the deduction from available evidence that pain, produced by different means, is processed differently in the central nervous system.

The superficial pain threshold to a thermal stimulus and the pain threshold to tibial pressure were examined in subjects given small amounts of nitrous oxide, halothane and sodium thiopental.

The thresholds moved in the same direction with nitrous oxide and halothane but moved divergently with sodium thiopental. It has been deduced that this differentiation is due to the difference in effect of barbiturates from other anesthetic drugs upon presynaptic inhibition in the spinal cord. Pain produced by a thermal stimulus to the skin and that produced by tibial pressure must be neurologically different.

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HYPOTHERMIA Lanatoside C in rats lowered the temperature required to cause death by two to five degrees centigrade. Electrocardiogram and blood pressure are not much changed but the fibrillatory threshold for serial electric stimulation is significantly raised. Digitalis may decrease permeability of membranes. (*Steinbereithner, K.: Influence of Lanatoside C on the Cooled Heart, Der Anaesthesist 13: 213 (July) 1964.*)

RESPIRATORY ARREST Curarized cats were studied during and after apnea preceded by ventilation with air. Blood pressure during apnea shows a typical biphasic behavior. First, there is a rise of blood pressure lasting one to two minutes, followed by a fall. In the third or fourth minute there is slowing of the heart. Blood pressure rises again after respiration is started. During apnea, carbon dioxide is accumulated in the body and alveolor carbon dioxide rises. With marked circulatory insufficiency there can be a discrepancy between carbon dioxide tensions in the blood and in the alveoli. As long as cardiac function following reventilation is poor, there is insufficient movement of carbon dioxide towards the lungs and expiratory carbon dioxide can fall below levels of the blood. As soon as circulation is improved, carbon dioxide is again better moved to the lung and blood becomes saturated with carbon dioxide. Five to fifteen minutes are required for complete elimination of retained carbon dioxide. A sudden decrease of the carbon dioxide concentration in expired air under conditions of constant ventilation signifies circulatory insufficiency. (*Wessig, H., and Tiedt, N.: Animal Experiments Concerning Circulation and Carbon Dioxide Elimination during and after Respiratory Arrest, Der Anaesthesist 13: 189 (June) 1964.*)