

EFFECTS OF LOW CONCENTRATIONS OF ENFLURANE ON PROBABILITY LEARNING

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SUMMARY

The effects of controlled subanaesthetic concentrations of enflurane on learning behaviour and on ability to change previously developed decision strategies were studied in 10 male volunteers, using a probability learning task. Subjects were instructed to predict on each of 200 consecutive trials, whether a left or a right light would appear. The appearance of lights was pre-determined by a set relative frequency unknown to the subject. The relative frequency was automatically changed at the end of the first 100 trials, from 8/10 lights in the left side to 4/10. It was found that enflurane at subanaesthetic concentration of 0.25% (end-tidal) slowed the rate of learning, and increased the number of trials required for readjusting the prediction strategy to the changed situation.

Subanaesthetic concentrations of general anaesthetic agents have been shown to affect various perceptual and cognitive functions such as sensory thresholds (Dundee, Nicholl and Black, 1962; Clark, Butler and Rosner, 1969), time perception (Robson, Burns and Welt, 1960; Adam, Castro and Clark, 1974), memory (Adam, 1973, 1976) and risk-taking in decision situations (Bentin, Collins and Adam, 1978). The anaesthetic effects are also reflected in electrophysiological correlates of sensory and cognitive processes (Clark and Rosner, 1973; Adam and Collins, 1978). With trace anaesthetic concentrations of halothane and nitrous oxide, Bruce and his colleagues (Bruce, Bach and Arbit, 1974; Bruce and Bach, 1975, 1976) have observed reduction of the digit span and impaired performance in tasks requiring divided attention; they have not found an influence on more complex cognitive functions such as observed with subanaesthetic doses. Trace anaesthetic concentrations may produce a very subtle effect which, although unmeasurable with currently available psychological tests, may add to other gas effects to result in a cognitive deficit.

Since gas concentrations that exist in the atmosphere of operating rooms are much less than those employed in the studies using subanaesthetic concentrations mentioned above (Frey et al., 1974),

the results obtained cannot be applied directly to the effects of trace anaesthetic concentrations on operating room personnel. Nevertheless, the value of studies using greater but still subanaesthetic concentrations of general anaesthetic agents should not be ignored. On the one hand, they may serve to indicate the type of cognitive impairment associated with general anaesthetics; on the other hand, they may suggest what brain structures are sensitive to anaesthetic effect, through known relationships between brain structure and functional deficit.

Small concentrations of general anaesthetic agents reduce the speed of acquisition of new material. This has been shown for both verbal (Steinberg and Summerfield, 1957; Parkhouse et al., 1960), and non-verbal material (Parkhouse et al., 1960). The most important aspect of behaviour in the operating room, however, is not always acquisition performance, but rather the need to adapt rapidly to new situations. The ability of the individual to adopt new strategies of behaviour in the face of change in available information is extremely sensitive to brain damage. It can be expected, therefore, that general anaesthetics, which affect the central nervous system, would have some deleterious effect on the appropriate behavioural response to relevant changes in the environment. We investigated the effects of subanaesthetic concentrations of enflurane on a probability learning task which has been used before to demonstrate rigidity of thought in brain-damaged individuals (Oscar-Berman, Sahakian and Wikmark, 1976). The task itself is simple and requires the subject to predict in each trial whether event A or event B will occur (Estes, 1964). The probability of each event to occur, not known to the subject, is governed by the

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experimenter, and is kept constant during a set of trials. A change in this probability brings about a change in the prediction offered by the subject (La Berge, 1959). The rate at which the subject achieves the new appropriate response may be used as a measure of behavioural rigidity, which is often termed "perseverative behaviour".

METHOD

Subjects

Ten paid student volunteers, 20–32 years old, gave informed consent to participate. Each subject underwent a complete physical examination, chest x-ray, e.c.g., routine haematological and urine analysis screening, determination of blood urea and serum glutamic oxaloacetic transaminase concentration. Only subjects within the normal range for each of these tests were accepted for study.

Procedure and materials

Eight of the 10 subjects formed the experimental group and two received placebo (compressed air breathed through the same circuit), believing that they were breathing an odourless gas. Each subject served as his own control, participating in two sessions "control" and "gas", separated by 4 days. Four subjects from the experimental group and one from the placebo group began the experiment with the gas session and the other five began with the control session. The subjects abstained from all solids, liquids and drugs 12 h before each session. Identical instructions were given at each session, before the inhalation procedure began. In the gas session, enflurane in air was vaporized in a Foregger copper kettle, and was delivered through a non-rebreathing circuit vented outside. The subject breathed the mixture through a mouthpiece connected to a Rahn end-tidal sampler. Inspired anaesthetic concentrations were adjusted individually so that the subject could still respond to stimuli and verbal commands. The mean concentration of enflurane was $0.25\% \pm 0.04\%$ (v/v). Inspired and end-tidal concentrations were measured to the nearest 0.005% by gas chromatography (Hewlett-Packard thermal conduction detector). End-tidal carbon dioxide was monitored continuously using a Beckman carbon dioxide analyser. Arterial pressure and heart rate were measured every 10 min, throughout the study. In the anaesthetic session, testing began only when the difference between end-tidal and inspired concentrations was less than 0.5%.

The probability learning task consisted of two green lights, 34 cm apart and a red warning light half-way between, all mounted on a black panel. In each trial the subject saw the red light first for 500 ms, then had to predict whether the green light would appear in the right or in the left side, by pressing either a right or a left switch. The time allowed for response was unlimited. Either the right or the left green light appeared according to a predetermined relative frequency of occurrence, 500 ms after the response was given. If, for example, the preset relative frequency was 8/10 left, eight randomly chosen trials in each 10 were left green. The next trial followed after a 1-s interval.

Two hundred consecutive trials were presented in each session. In the first session, whether gas or control, the relative frequency of the left green light to appear was 8/10 for the first 100 trials, but only 4/10 for the remaining 100 trials. In the second session, the same relative frequencies were used for the right green light. The subject had no advance knowledge of the change.

An anaesthetist supervised the entire session and the subject remained under medical observation for 30 min following the end of the experiment.

RESULTS

Inhalation of low concentrations of enflurane (about 0.25% end-tidal) impaired both the initial learning behaviour and the adaptation to changes in situational factors. The data from each subject were analysed as follows. The subject's responses from each session were in groups of 10 trials each, that is the first 10 predictions formed the first group, the second 10 formed the second group, and so on. Each 10-trial group provided one data point—the frequency of left green predictions. For example, if, in the first 10 trials, the subject predicted left on five trials, the data point would show 0.5 (50%) subjective probability. Objective probability was always 0.8 for the first 10 groups (100 trials) and 0.4 for the last 10 groups. The subjective probability curves over all eight subjects for both control and gas sessions are shown in figure 1. The regression curves best fitting the data were found to be polynomials of the third order (fig. 2).

Enflurane effects on learning behaviour

The rate of initial learning was significantly slower for the anaesthetic condition, as reflected by less steep slopes of the learning curves, measured after 20 trials ($P < 0.01$, two-tailed *t* test). The learning curves reached their asymptote (steady state) after about 50

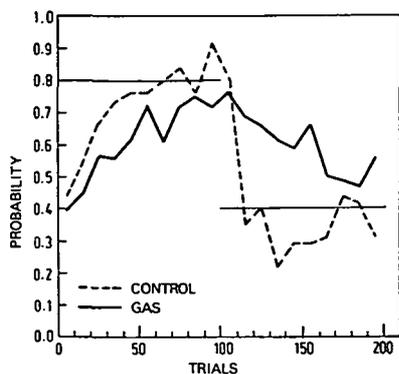


FIG. 1. Average probability of prediction of left light appearance per group of 10 trials averaged for eight subjects. The thick broken line shows control data and the thick solid line the anaesthetic data. The thin solid line shows the actual (objective) probability of left light appearance, being 0.8 for the first 100 trials and 0.4 for the last 100 trials.

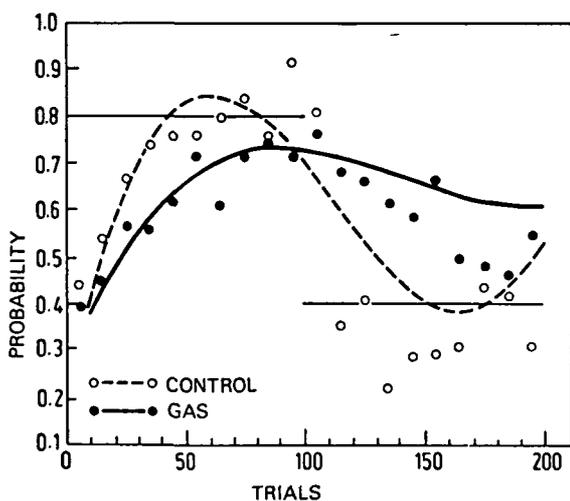


FIG. 2. Regression curves best fitting the data shown in figure 1. The curves are polynomials of the third order. The broken and solid lines are for control and anaesthetic data respectively.

trials in both control and gas sessions (at this stage, the slopes of all curves did not differ significantly from 0). The level of the predicted relative frequency at the steady state was significantly higher in the control ($P < 0.025$, Wilcoxon test). Since the ideal performance in this task was to predict constantly the side with the higher frequency (Goodnow, 1955), learning was considered to be more efficient in the control sessions.

Effects on rigidity of thought

In control sessions, the change induced in the objective probability was followed by an immediate change in the subject's prediction strategy. In contrast, no such immediate change was found with enflurane (fig. 1). Perseverative behaviour was assessed by the number of trials until subjective probability was one standard deviation less than the former steady-state level. With enflurane the subjects required significantly more trials to reach this level ($P < 0.01$, two-tailed t test). An additional index of perseveration was the slope of the regression curves 10 trials following the change in objective probability; faster adaptation to the new situation is reflected by a steeper decrease of predicted probability functions. The slopes calculated for control data had significantly greater absolute values than those obtained in the anaesthetic group ($P < 0.001$, two-tailed t test).

Data from the anaesthetic session for the placebo group did not differ significantly from data obtained in control sessions, when comparing either the first or the last 100 trials (fig. 3).

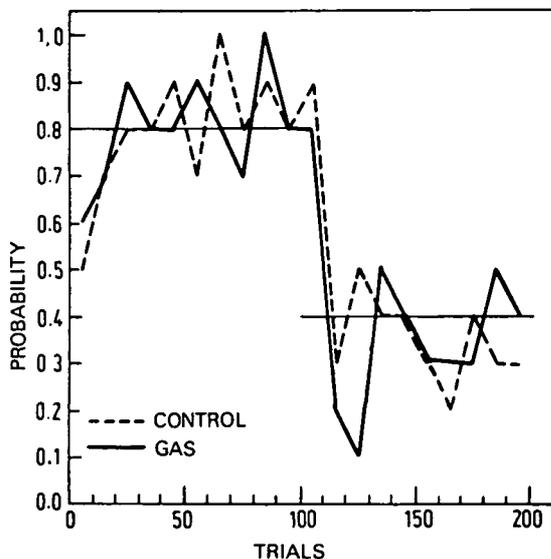


FIG. 3. A display as in figure 1, but for the two subjects who received the placebo. The thick broken line shows data for the control session and the solid line for the pseudo-gas session, where subjects breathed compressed air instead of enflurane.

DISCUSSION

Low concentrations of enflurane decreased the rate, and impaired the efficiency of learning. Moreover, enflurane increased considerably the number of trials

required for changing a previous response strategy, possibly reflecting a rigidity of thought.

The negative influence of enflurane on the rate of learning cannot be explained solely by impairment of attentional mechanisms. Electrophysiological findings in man (Adam and Collins, 1978) suggest that enflurane decreases the rate of information processing, which might partly account for the slower learning. Difficulty in changing a response strategy might indicate a generalized mental and behavioural rigidity (perseveration); alternatively, the results may be explained by a delay in grasping situational changes, this being induced by impairment of information processing. Both interpretations are supported by the literature, suggesting that both factors may act concomitantly.

Slower learning rates have been observed with other inhalation anaesthetic agents for both verbal and pictorial material (Steinberg and Summerfield, 1957; Parkhouse et al., 1960). This may suggest that the anaesthetic influence on learning is not specific to enflurane, but a general effect of anaesthetic drugs acting on the brain. More specificity might exist in the susceptibility of different brain areas to anaesthetics. Similar perseveration, assessed with the same task, was described in patients suffering from alcoholism and Korsakoff's syndrome, in whom anatomical lesions occur in the limbic system (Oscar-Berman, Sahakian and Wikmark, 1976). In rats, a lower final performance level in a maze learning task and perseveration were found after various damage to the hippocampus (Stevens and Cowey, 1973; Nonneman, Boigt and Kolb, 1974). Since both human and animal studies implicate dysfunction of the limbic system in impaired learning and perseveration, one may speculate that limbic and related cortical structures are particularly sensitive to anaesthetic agents.

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EFFETS DES FAIBLES CONCENTRATIONS
D'ENFLURANE SUR LES CALCULS DE
PROBABILITES

RESUME

On a étudié sur 10 volontaires mâles, à l'aide d'un exercice comportant des calculs de probabilités, les effets des concentrations sous-anesthésiantes contrôlées d'enflurane sur le comportement de la faculté d'apprendre et sur la possibilité de modifier les stratégies de décision précédemment mises au point. Les sujets ont été priés de prédire pour chacun de 200 essais consécutifs, si l'on verrait une lumière à droite ou à gauche. L'apparition des lumières avait été prédéterminée par une fréquence relative fixée, inconnue du sujet. La fréquence relative a été automatiquement modifiée à la fin des 100 premiers essais, passant de 8/10 lumières du côté gauche à 4/10. On a trouvé que l'enflurane à des concentrations sous-anesthésiantes de 0,25% (volume final) ralentissait le taux auquel on peut apprendre et augmentait le nombre des essais requis pour réajuster la stratégie de prédiction à la situation modifiée.

WIRKUNGEN GERINGER KONZENTRATIONEN
VON ENFLURAN AUF DIE LERNBARKEIT VON
WAHRSCHEINLICHKEITEN

ZUSAMMENFASSUNG

Die Wirkungen von kontrollierten, subanästhetisierenden Konzentrationen von Enfluran auf das Lernverhalten und auf die Möglichkeit, früher entwickelte, strategische Entscheidungen abzuändern wurde in 10 Männern, die sich dem Test aus freien Stücken unterzogen, untersucht. Dazu wurde eine Wahrscheinlichkeitslernaufgabe benutzt. Die Testpersonen wurden instruiert, in 200 aufeinander

folgenden Versuchen vorauszusagen, ob ein Licht links oder rechts erscheinen würde. Das Erscheinen des Lichts war durch eine festgesetzte, relative Häufigkeit, die der Testperson unbekannt war, vorausbestimmt. Diese relative Häufigkeit wurde automatisch nach den ersten 100 Versuchen von 8/10 Lichterscheinungen auf der linken Seite auf 4/10 geändert. Es wurde gefunden, dass Enfluran bei einer subanästhetisierenden Konzentration von 0,25% (end-tidal) die Lernbarkeit von Wahrscheinlichkeiten verlangsamte, und die Zahl der benötigten Versuche, um die Voraussagestrategie an die veränderte Situation anzupassen, musste erhöht werden.

LOS EFECTOS QUE EJERCEN PEQUEÑAS
CONCENTRACIONES DE ENFLURANO SOBRE
EL APRENDIZAJE DE PROBABILIDADES

SUMARIO

Se estudiaron los efectos que ejercen concentraciones sub-anestésicas controladas de enflurano sobre el comportamiento de aprendizaje y la habilidad de cambiar estrategias anteriormente desarrolladas para la adopción de decisiones en 10 voluntarios masculinos, mediante la aplicación de una tarea de aprendizaje de probabilidades. Se instruyó a los sujetos a que predijeran en cada una de 200 tareas consecutivas, si se encendería una luz a la izquierda o a la derecha. El encendido de luces estaba predeterminado por una frecuencia relativa desconocida por el sujeto. La frecuencia relativa fue cambiada automáticamente al cabo de las primeras 100 pruebas, de 8/10 luces al lado izquierdo a 4/10. Se descubrió que el enflurano en una concentración subanestésica de 0.25% (final de marea) redujo la rapidez de aprendizaje y aumentó la cantidad de pruebas necesarias para reajustar la estrategia de predicción a la nueva situación.