Laboratory Investigations

Rats show unimpaired learning within minutes after recovery from single bolus propofol anesthesia

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Purpose: To examine the learning ability of rats shortly after recovery from a bolus dose of propofol by assessing learning on a swim-to-platform task. Also, muscarinic blockade was used as a pharmacological test of whether learning shortly after propofol anesthesia resembles normal learning.

Methods: Propofol anesthetized rats (15-20 $mg \cdot kg^{-1}$ *iv*) were trained on a swim-to-platform task five to seven minutes after recovering from surgical anesthesia and tested two to three hours later. In addition, the muscarinic antagonist scopolamine hydrobromide (5 $mg \cdot kg^{-1}$ *sc*) was given to a subgroup of rats before testing. During 10 trials, the number of times a given rat took 10 sec or longer to locate and climb onto a visible platform was tabulated and counted as errors.

Results: When trained shortly after recovery from the anesthetic, propofol anesthetized rats made 3.2 ± 0.4 compared with 1.0 ± 0.1 errors in controls ($P < 0.0001$). Two to three hours later both groups performed equally well. Rats trained after propofol anesthesia and given scopolamine before testing made 0.7 ± 0.5 errors and performed as well as normal controls, 1.2 ± 0.2 errors when subjected to the same procedures without propofol anesthesia, and better than scopolamine-treated untrained rats, 5.5 ± 0.7 errors, ($P < 0.05$).

Conclusion: Training five to seven minutes after recovery from propofol anesthesia resulted in normal retention of the swim- to-platform task. It also produced the same resistance to the disruptive effects of scopolamine as did training in rats that were not anesthetized. Thus, the ability to learn recovers rapidly after propofol anesthesia induced by a single intravenous bolus dose.

Objectif : Examiner la capacité d'apprendre des rats, peu après la récupération d'une anesthésie avec une dose bolus de propofol, en évaluant comment ils apprennent à nager vers une plate-forme. De plus, utiliser le blocage muscarinique en qualité de test pharmacologique de l'apprentissage, et voir si c'est comparable à un apprentissage normal.

Méthode : Des rats ayant reçu une anesthésie au propofol (15-20 $mg \cdot kg^{-1}$ *iv*) ont été entraînés à nager vers une plate-forme, cinq à sept minutes après la récupération de l'anesthésie et ont été testés de nouveau deux à trois heures plus tard. La scopolamine, antagoniste muscarinique, a été administrée (5 $mg \cdot kg^{-1}$ sc) à un sous-groupe de rats avant les essais. Pendant les 10 essais, le nombre de fois qu'un rat donné prenait 10 s ou plus pour atteindre une plate-forme visible et y grimper ont été considérées comme des erreurs.

Résultats : Les rats entraînés peu après la récupération de l'anesthésie au propofol ont fait 3,2 ± 0,4 erreurs et les rats témoins, 1,0 ± 0,1 erreur ($P < 0,0001$). Deux ou trois heures plus tard, les performances étaient égales pour les rats des deux groupes. Les rats entraînés après l'anesthésie et qui ont reçu de la scopolamine avant les essais ont fait 0,7 ± 0,5 erreur, faisant aussi bien que les rats témoins, 1,2 ± 0,2 erreur, soumis aux mêmes épreuves sans anesthésie au propofol, et mieux que les rats non entraînés mais traités à la scopolamine, 5,5 ± 0,7 erreurs ($P < 0,05$).

Conclusion : L'entraînement, cinq à sept minutes après la récupération de l'anesthésie au propofol, a permis une rétention normale de l'apprentissage qui consistait à nager vers une plate-forme. Cela a produit aussi la même résistance aux effets perturbateurs de la scopolamine que l'entraînement des rats non anesthésiés. Ainsi, la capacité d'apprendre est rapidement récupérée après l'anesthésie au propofol induite avec une dose unique en bolus intraveineux.

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PROPOFOL administration results in rapid induction of anesthesia, absence of excitatory effects, rapid recovery and no ill aftereffects.[1] The drug exhibits both a rapid onset and short duration of action, which has allowed it to become one of the most commonly used anesthetics in day case surgery.[2,3]

The effects of propofol on behavioural abilities in the immediate post-surgical period have not been fully determined. Comparisons with baseline values and/or unanesthetized volunteers suggest that psychomotor function (i.e. behaviour mediated by cerebral activity) is impaired both during propofol sedation[4,5] and for up to five hours after propofol anesthesia.[2] It has been suggested that short term and working memories are most affected in the recovery phase[6] but that implicit memory may be spared throughout both surgery and recovery.[4,6,7] Studies which examined recovery after prolonged infusions of propofol suggest that a minimum of three hours is needed for complete cognitive recovery from the anesthetic.[8] However, cognitive recovery times from a single intravenous bolus dose have not been determined. Such doses are commonly used for minor procedures such as examinations under anesthesia (EUA), and dilatation and curettage. Propofol in single bolus doses has also become the drug of choice for certain therapeutic interventions such as cardioversion.

The present study has attempted to address the issue of cognitive recovery from propofol in an animal model. This was done by training rats on a simple learning task shortly after recovery from a single intravenous dose of propofol and then testing retention several hours later.

Learning was also assessed using a pharmacological test. Animals given antimuscarinic drugs, such as scopolamine, are typically impaired on novel tasks but unimpaired on familiar tasks. A dose of 5.0 $mg \cdot kg^{-1}$ scopolamine *sc* in rats has been shown to produce total blockade of the cholinergic component of electrocortical activation and to impair swim-to-platform behaviour severely in untrained rats.[9–12] This effect has also been demonstrated on tests of passive avoidance,[13] active avoidance[9,14] and escape from a narrow alley[15] but the mechanism of the effect is not understood. It is possible that scopolamine interferes with the development of an engram (i.e. neural changes due to learning) but has no effect on its later expression.[9,16] Regardless, scopolamine has been shown to severely impair the acquisition of a learned response but to have very little effect on retention.[9,10,13–15] Thus, training-induced resistance to the behaviour-disrupting effect of scopolamine could be used as a pharmacological test of whether learning initiated shortly after recovery from propofol anesthesia has properties similar to learning initiated in undrugged animals. As there appear to be no systematic data on the effects of different degrees of training on resistance to the disruptive effect of central muscarinic blockade, a preliminary experiment was done to determine how much training is needed to produce such resistance.

Methods

Subjects

The methods used were approved by the Animal Use Subcommittee of the University of Western Ontario. Experiments were carried out on 142 male hooded or albino rats weighing 265-760 g. The rats were maintained on a 12:12 hr light-dark cycle with food and water freely available. Training and testing were done in the light phase. In eight cases, rats had previous swimming experience in the Morris water maze[17] but there is no transfer of learning from this task to the swim-to-platform task used here.[18] All other rats in the study were naive and none had any previous drug experience. All rats were randomly assigned to drug treatment groups and rats from different groups were tested successively in an irregular order.

Swim-to-platform task

Rats were trained to swim to a platform in the centre of an aquarium 43 × 90 × 45 cm deep and filled with clean water to a depth of 25 cm. The platform was an overturned wire mesh rat cage with its upper surface measuring 21.5 × 18.5 cm and raised 1 cm above the water. On each trial, a rat was released into the tank facing one corner and the time taken until it had all four feet on top of the platform was measured with a stop-watch. If a rat failed to climb up within 60 sec it was manually placed on the platform. Swim times of 10 sec were considered to be errors. An additional measure which was also taken was the number of passes, which was defined as the number of times the rat swam the long axis of the tank and passed by the platform with all four feet.

During the acquisition phase, in which rats were first introduced to the task, 10 trials per rat were given with an intertrial interval of 10-20 sec. Each rat was then dried with paper towels, warmed with a 100 W incandescent light and allowed to rest for two to three hours before a second block of 10 trials was given (retention phase). Rectal temperature was taken after acquisition and before and after retention (6.5 cm penetration). Since core temperature below about 30°C impairs swim-to-platform performance,[19] testing was begun only when the core temperature was at least 36°C.

Previous studies have shown that performance on the retention phase in normal rats was similar when intervals between the acquisition and retention phases ranged from 15 min to one week.[9,16,20]

Procedure

PRELIMINARY STUDY. A preliminary study was performed to determine the number of trials needed to produce resistance to the disruptive effects of scopolamine on performance in the swim-to-platform task. This was accomplished by varying the amounts of training the rats received. Male hooded or albino rats were trained in the swim-to-platform task (described above) in 24°C water. Different groups of rats (n=10 per group) were given 0, 1, 5, 10, 20 or 30 training trials in a single session. Twenty four hours later the rats were given 5.0 mg·kg^{-1} scopolamine hydrobromide *sc* followed, after a delay of 15-30 min, by 10 trials in the aquarium. Additionally, a control group of saline injected rats (n=10) along with a third group which received no injections (n=17) were run for one block of 10 trials.

This preliminary study determined that 10 trials of training produce maximal resistance to the disruptive effects of scopolamine on performance in this task (see Results). Based on this, 10 trials were used during both the acquisition and retention phases for the primary study.

PRIMARY STUDY. Training and testing were both carried out in water at 20°C. The difference in water temperature between the two studies (4°C) would not have had any effect on performance.[16] Before training, 25 of the rats received 15-20 mg·kg^{-1} propofol (Diprivan; 10 mg·ml^{-1}) injected into the saphenous vein of the hind leg. The depth of anesthesia during injection was assessed by corneal and pinna reflexes, and the injection was halted temporarily if both reflexes disappeared.

In five cases, the rats were restrained in a canvas hammock and given 0.2 ml lidocaine hydrochloride 1.0% *sc* on each side of the saphenous vein injection site 10 min before the propofol injection. As this was a difficult method of administering the drug, the injection procedure was changed and other unrestrained rats (n=20) were lightly anesthetized with diethyl ether before receiving propofol. As training occurred approximately 30 min after the onset of propofol anesthesia and the effects of ether are very short, this was considered a viable alternative to the injection method using the hammock. No performance differences between these subgroups were apparent. The remaining control rats were either: (a) lightly anesthetized with ether and given saline (equivalent volume) in the saphenous vein (n=5); (b) given 1.0 ml·kg^{-1} saline (*sc* in nape of neck; n=10); or (c) received no treatment (n=15) (Table - Treatment #1).

TABLE Drug treatments per group before acquisition and retention trials of the swim-to-platform task. Drugs were given intravenously (*iv*), subcutaneously (*sc*) or by inhalation (ether). Acquisition training followed Treatment #1 and retention testing followed Treatment #2. Scop, scopolamine.

Group	*n*	*Treatment #1 (before acquisition)*	*Treatment #2 (before retention)*
1	13	propofol (*iv*)	nil
2	7	propofol (*iv*)	scop (*sc*)
3	5	propofol (*iv*)	saline (*sc*)
4	5	ether + saline (*iv*)	nil
5	10	nil	nil
6	5	nil	saline (*sc*)
7	10	saline (*sc*)	scop (*sc*)

During the acquisition phase, swim-to-platform training began in propofol-injected rats five to seven minutes after the recovery of the righting response (ie. the point when the rat regained the ability to right itself onto all four paws from a supine position). In the first 10 rats, the average duration of anesthesia was 23 min from start of injection to return of righting. This was used as a baseline and control rats which received saline were trained 28-30 min after injection. Exactly 15 min before the retention phase, rats received either: (a) 5.0 mg·kg^{-1} scopolamine hydrobromide (*sc* in nape of neck; n=17); (b) an equivalent volume of saline (*sc*; n=15); or (c) no injection (n=23) (Table - Treatment #2).

Statistics

All data were analysed non-parametrically using the Kruskall-Wallis one-way analysis of variance, the Mann- Whitney U-test and Spearman's rank order correlations.[21] Data are represented by means ± standard errors of means (SEM).

Results

PRELIMINARY STUDY. Performance during retention following scopolamine treatment varied as a function of the amount of training (Kruskall-Wallis; $P < 0.0001$). Untreated hooded rats (n=10) made 1.2 ± 0.1 errors in 10 trials. Untreated albino rats (n=7) performed equally well, making 1.2 ± 0.2 errors. In contrast, rats given an injection of scopolamine 15-30 min before training (n=10) made 5.5 ± 0.7 errors, differing from the untreated rats ($P < 0.01$). The injection procedure had no effect in itself since a saline injection

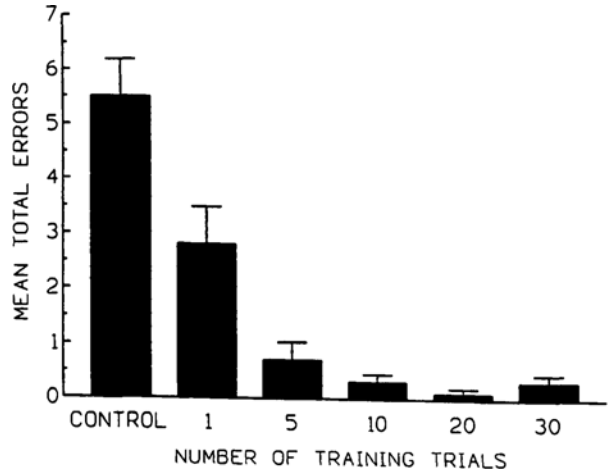

FIGURE 1 Errors made in blocks of 10 trials in the swim-to-platform task by scopolamine-treated rats 24 hr after a varying number of training trials. Scopolamine was given 15-30 min before the data shown were collected. Controls received no previous training on the task. The numbers of the other groups represent the number of training trials each previously received. Each group: n=10.

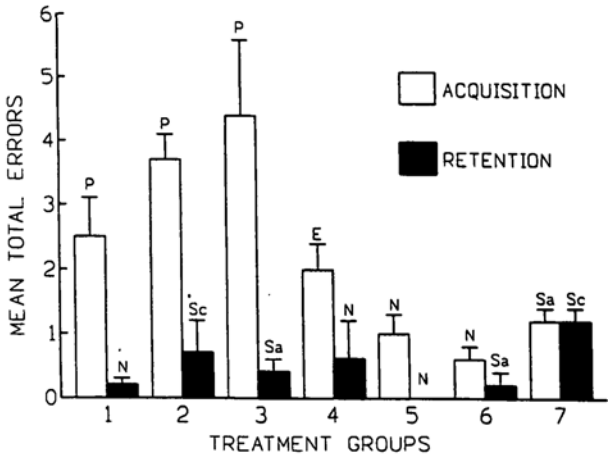

FIGURE 2 Errors made in blocks of 10 trials in the swim-to-platform task by rats treated with various drugs. White: acquisition. Black: retention. Drugs or drug vehicle injections were given approximately 30 min before acquisition or 15 min before retention. Group 1: n=13; Acquisition, after ether plus propofol (n=8) or after lidocaine plus propofol (n=5); Retention, after no additional drug treatment. Group 2: n=7; Acquisition, after ether plus propofol; Retention, after scopolamine. Group 3: n=5; Acquisition, after ether plus propofol; Retention, after saline *sc*. Group 4: n=5; Acquisition, after ether plus saline *iv*; Retention, after no additional drug treatment. Group 5: n=10; Acquisition, after no drug treatment; Retention, after no additional drug treatment. Group 6: n=5; Acquisition, after no drug treatment; Retention, after saline sc. Group 7: n=10; Acquisition, after saline sc; Retention, after scopolamine. P, propofol; N, no treatment; Sc, scopolamine; Sa, saline; E, diethyl ether.

15-30 min before training resulted in 1.5 ± 0.3 errors (n=10) (data not shown).

After scopolamine, rats given one previous training trial outperformed those with no previous training ($P < 0.05$) and rats given five training trials made fewer errors than those given one training trial ($P < 0.05$). Furthermore, rats given 10 training trials outperformed those given one training trial ($P < 0.01$) but did not differ from rats which received five training trails. As performance did not improve beyond 10 training trials (Figure 1), 10 trials were used for both the acquisition and retention phases of the main study.

PRIMARY STUDY. Injection of a bolus of propofol in conscious rats, restrained in a hammock (n=5) and locally anesthetized with lidocaine, produced deep anesthesia with a rapid onset and a duration of 22.0 ± 2.9 min from the start of injection to the recovery of the righting response. Propofol was injected slowly over 5.2 ± 0.8 min in rats lightly anesthetized with ether (n=20). These rats had a mean recovery time of 25.9 ± 1.3 min which did not differ from rats given propofol without ether ($P > 0.10$:NS). The mean recovery time of rats given saline during light ether anesthesia (n=5) was 4.0 ± 0.5 min, which was much faster than the recovery time of rats given propofol (n=25; $P < 0.001$).

Of the 25 rats which received propofol, 12 twitched their heads and/or kicked one or both hind legs as they emerged from propofol anesthesia. Immediately upon righting 10 rats tried to run at full speed, though quite ataxic. Neither of these effects was seen in rats given ether plus saline (n=5). Propofol-anesthetized rats swam well when trained five to seven minutes after the recovery of righting, though all were unsteady when climbing the platform and 18 fell off one or more times after they had climbed on. When this happened the rat was placed back on the platform.

Performance on the swim-to-platform task did not differ between rats given propofol during restraint with lidocaine treatment (n=5) and those given propofol during light ether anesthesia (n=8; $P > 0.10$). Therefore, these subgroups were combined (total n=13) to form Group 1 which received propofol prior to acquisition and no specific treatment prior to reten-

tion. Group 2 (n=7) received propofol prior to acquisition and scopolamine prior to retention. Group 3 (n=5) received propofol prior to acquisition and saline prior to retention. Group 4 (n=5) received saline during light ether anesthesia prior to acquisition and no specific treatment prior to retention. Group 5 (n=10) received no specific treatment prior to either acquisition or retention. Five of these rats had previously been trained in a Morris water maze and five had no such training. As expected, these subgroups did not differ during acquisition or retention so they were combined into a single control group. Group 6 (n=5) received no treatment prior to acquisition and saline prior to retention. Group 7 (n=10) received saline prior to acquisition and scopolamine prior to retention (Table).

A Kruskall-Wallis 1-way analysis of variance indicated that differences existed among Groups 1-7 during acquisition ($P < 0.001$). Follow up Mann-Whitney U-tests revealed that rats which received no drug treatment before acquisition (Groups 5-7) did not differ in performance during acquisition. Since Groups 1-3, which were given propofol before acquisition, also did not differ from one another they were combined and compared with Groups 5-7, which were similarly combined. Rats which had recently recovered from propofol anesthesia made 3.2 ± 0.4 errors and were clearly impaired compared with the drug-free rats which made 1.0 ± 0.1 errors during acquisition ($P < 0.0001$). In addition, each of Groups 1-3 were impaired in performance compared with each of Groups 5-7 ($P < 0.05$ or better in all cases). Rats trained after ether anesthesia without propofol (Group 4) made 2.0 ± 0.4 errors and performed worse than Groups 5-7 ($P < 0.05$) but did not differ from Groups 1-3 during the acquisition phase (Figure 2).

During the retention phase, differences were again present among groups ($P < 0.01$; Kruskall-Wallis). This was due primarily to Group 7 which received scopolamine before retention and made 1.2 ± 0.2 errors during retention testing. These rats performed worse than each group not treated with scopolamine ($P < 0.05$), with the exception of Group 4. Group 2, which underwent propofol anesthesia and were given scopolamine prior to retention testing, made 0.7 ± 0.5 errors during retention testing. These rats did not differ in performance from any other group, including groups that were drug-free throughout the retention phase. No other differences existed among groups (Figure 2). Of particular interest, propofol anesthetized rats which did not receive scopolamine (Groups 1 and 3) made 0.2 ± 0.1 errors during the retention phase and performed better than drug-free rats (Groups 5-7) performed during the acquisition phase ($P < 0.01$).

Examining the primary study as a whole, errors and passes correlated highly during the acquisition phase (0.77) and very highly during the retention phase (0.97) (Spearman's correlation coefficients; $P < 0.001$). For the preliminary study, the number of errors also correlated very highly (0.98) with the number of passes made ($P < 0.001$).

Discussion

The duration of propofol induced anesthesia, both with and without ether, was similar to that reported by Fassoulaki *et al.* of 25.9 min for the same dose.[22] Surgical anesthesia in the rat may be obtained with a propofol dose as low as 10 $mg \cdot kg^{-1}$ but such anesthesia typically lasts only 60-90 sec.[23] A dose of 40 $mg \cdot kg^{-1}$ resulted in the death of five of six rats.[23] Several investigators have reported the appropriate *iv* dose of propofol for surgical anesthesia in rats to be 20 $mg \cdot kg^{-1}$ [22,24] and this study supports that value. Rats given saline while lightly anesthetized with ether recovered in about four minutes.

Rats in this study responded to propofol in the manner described by previous authors. The twitching and kicking seen upon recovery from propofol has been previously reported in mice.[25] It has been suggested that this is due to glycine antagonism[2,25] and possibly to a desensitization of GABAergic pathways[26] which may produce a refractory state at the level of receptors. Although propofol studies in humans have revealed that myoclonic or seizure activity[27] is rare, there are several case reports of seizure-like movements after propofol.[26,28]

Rats which were trained five to seven minutes after recovering from propofol anesthesia (Groups 1-3) were clearly impaired on the swim-to-platform task. Similarly, rats were impaired in swim-to-platform performance shortly after recovery from ether anesthesia but the effects of ether and propofol together were no greater than those of either anesthetic alone. This lack of synergistic effect probably reflects the brevity of ether anesthesia, as the cognitive and psychomotor effects of propofol are typically additive with other anesthetics.

When tested two to three hours later, the rats that had been anesthetized with propofol performed as well as rats which were drug-free throughout this study. Furthermore, they performed better on the retention phase than drug-free rats did on the acquisition phase. This indicates that despite initially impaired performance, rats recovering from propofol anesthesia benefited from training and normal learning did occur.

Another way to assess learning and memory is to administer anti-muscarinic drugs (eg. scopolamine)

which produce marked impairments on acquisition of a learned behaviour but have less effect on a well-established conditioned behaviour. To determine the effect of different degrees of training on resistance to the disruptive effect of central muscarinic blockade, rats received varying amounts of training on the swim-to-platform task (0, 1, 5, 10, 20 or 30 trials) and then swam 10 trials after receiving scopolamine. Even one training trial in the normal state had a strong effect but additional training further reduced the disruptive effect of scopolamine on retention and a ceiling effect was reached at 10 trials after which rats did not improve further. These results provide further evidence that scopolamine disrupts performance on novel tasks but has less effect on previously learned tasks. Moreover, this effect varies with the amount of training received prior to drug treatment. This experiment provided the basis for the use of 10 trials to test for resistance to the disruptive effects of scopolamine in rats receiving training shortly after propofol anesthesia compared with normal rats.

If learning which occurs shortly after recovery from propofol anesthesia is defective in some way, subsequent retention testing might reveal an increased sensitivity to the effects of scopolamine. No such effect was found. Ten trials of training shortly after recovery from propofol anesthesia produced much the same resistance to the disruptive effects of scopolamine as 10 trials in the normal state. Thus, the poor acquisition performance seen in propofol anesthetized rats was likely due to psychomotor deficits rather than impairment of the learning process itself.

It should be noted that the swim-to-platform task is relatively simple and, thus, may not be sufficiently sensitive to test for the possible detrimental effects of recent anesthesia with propofol. However, it may be pointed out that this test is sensitive to a variety of cognitive impairments such as to the effects of scopolamine in a dose dependent manner,[12] and also to hypothermia,[19] and to large lesions of the medial thalamus or the mamillary bodies or to combined lesions of the hippocampus, posterior neocortex and amygdala.[29]

Clinical studies have suggested that a minimal time of three to five hours is needed for complete cognitive recovery from prolonged propofol anesthesia.[2,8] However, the results from this study indicate that normal learning may occur within a matter of minutes after recovery from a single bolus dose of propofol. This has positive implications for post-anesthetic patient care related to minor procedures or therapeutic interventions which use single doses of propofol.

In summary, rats trained on a swim-to-platform task five to seven minutes after recovery from propofol anesthesia demonstrated normal retention when tested two to three hours later. Additionally, training produced the same resistance to the disruptive effects of scopolamine as did training in rats which were not anesthetized at all. This indicates relatively normal learning can occur within minutes after recovery from a single bolus infusion of propofol. If humans are comparable to rats in this respect, this suggests that patients may be capable of retaining information, such as follow up directions or answers to medical questions, shortly after recovery from single bolus propofol anesthesia.

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