Memory functions during propofol sedation do not differ between smokers and non-smokers

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There is no conflict of interest.

Summary

Objective: To study the influence of chronic smoking on explicit learning abilities, during propofol sedation.

Methods: For 24 smokers and 25 matching non-smokers, learning performance was evaluated during three increasing depths of propofol sedation. Twenty-four hours after anaesthesia, delayed performances (recall and recognition) were assessed. Recognition scores were computed using both raw data and a validated recognition discriminability index *(d')*, which took false recognitions into account.

Results: Learning performances during propofol induction were equal in both groups: 21 words recalled from 24 presented words (range in smokers 14 to 24 words, in non-smokers 13 to 24 words [$p = 0.58$]). No differences were observed in recall, 24 h after anaesthesia: median recall of the 24 words was 7 words in smokers (range, 13 to 24), and 6 words in non-smokers (range, 3 to 10) ($p = 0.58$). Increasing depth of sedation decreased learning performances in both groups but did not reveal differences in learning or recall performances between smokers and non smokers. In the delayed recognition task, there was no difference in the number of correct recognitions in both groups (smokers, 16 ± 4.8 words from 24; non-smokers, 15.8 ± 4.5; $p = 0.86$), neither interaction between sedation stage, groups and performances. Only *d'* was lower (1.9 ± 0.6) for smokers, than for non-smokers (2.8 ± 1.5; p = 0.019). Post hoc analyses showed a higher number of false recognitions in smokers (4.7 ± 3.9) than in non-smokers (2.4 ± 2.9; $p = 0.029$).

Conclusions: Otherwise healthy, chronic smokers undergoing propofol-based general anaesthesia present no differences in explicit memory abilities compared with matched, non-smoking controls, except for a slight but significant increase in false recognition.

Key words: nicotine; learning performance; long-term recognition

Introduction

Chronic smoking is associated with an acceleration of cognitive decline in non-demented, elderly subjects [1]. That decline seems to be clinically relevant essentially after the age of 75, since no difference was found in memory performances between smokers and non-smokers until 75 years of age [2]. However, some data suggest that chronic smoking is associated with a subtle cognitive decrease, even in young smokers, implicating executive functions and memory [3]. These modifications may be associated, not only with well-known cerebro-vascular changes, but also with up-regulation and desensitisation of Nicotinic acetylcholine receptors (nAChRs), as well as enhancement of GABA-ergic transmission in the brain [4, 5], which are both involved in several cognitive functions like attention, learning and working memory [6]. Therefore, some concerns have been raised that chronic smoking and abstinence from smoking before an anaesthesia may influence peri-anaesthetic amnesia, particularly when propofol is used. Apart from its anaesthetic values, propofol, a positive allosteric modulator of the $GABA_A$ receptor, is known to dramatically impair explicit learning, recall and recognition, and some of these effects can persist for more than 24 hours [7]. Such amnesia is an important part of patients' comfort during sedation and there is a current interest to find predictors of recall capacities in patients who undergo propofol anaesthesia [8]. We have recently reported on the impact of the smoking status of surgical patients on hypnotic properties of the intravenous anaesthetic propofol [9]. Using the same patient population, we studied the effect of chronic smoking on learning performance during increasing depths of propofol sedation, and on recall and recognition 24 hours after propofol administration. We hypothesised that chronic nicotine intake would modify memory function in patients receiving propofol [10, 11].

Methods

The Institutional Ethical Committee approved this protocol. We included native French-speaking patients of both genders, between 18 and 60 years of age, who were scheduled to undergo elective minor surgery under a standardised general anaesthetic with orotracheal intubation [9]. Surgical interventions were septoplasties and/or turbinoplasties (16 non-smokers and 14 smokers) and lumbar discectomies (9 non-smokers and 11 smokers). All patients gave written informed consent. Exclusion criteria were a past history of neuropsychiatric, cardiac or cerebrovascular events, developmental disorders, changes in leisure and/or professional activity during the last year, absence of physical activity [12], intake of drugs that may have a synergistic hypnotic effect

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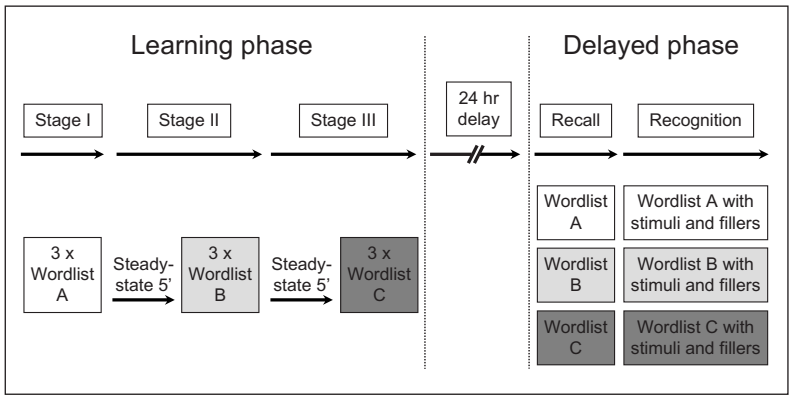
Figure 1 Learning and delayed memory procedure. Stage I: propofol effect-site concentration, 0.0 µg/ml (baseline); Stage II: propofol effect-site concentration, 0.7 µg/ml; Stage III: propofol effect-site concentration, 1.1 µg/ml. Word lists A to C ("targets"), and stimuli (systematically related to targets) and fillers (unrelated to targets) were composed of 24 words each.



with propofol and any contraindication to a slow anaesthesia induction procedure. For each eligible smoker, a non-smoking control, matched for gender, age, height, weight, type of surgery, and socio-cultural background, was recruited. To compare socio-cultural background education, levels were scored on a 3-point scale (1 = ≤9 years; 2 = 9 to 12 years; 3 = ≥12 years of education). A smoker was defined as having smoked at least 20 cigarettes per day during the last two or more years. The degree of cigarette consumption was expressed as pack-years; that is the number of cigarette packs smoked per day multiplied by the number of smoking years. Smokers were requested to refrain from smoking the day of surgery.

The study was carried out in a prospective, controlled, single blinded manner. No pre-medication was given. Standard, non-invasive anaesthesia monitoring was used. Propofol was administered intravenously using the pharmacokinetic model by Schnider et al. [13]. This model estimates the plasma and cerebral propofol concentrations. The estimated cerebral concentration of propofol was used as a surrogate to quantify the hypnotic effect of propofol.

Evaluation of specific memory tasks was conducted before administration of propofol (baseline, stage I) and after having obtained an estimated cerebral (i.e., effect-site) propofol concentration of 0.7 µg/ml (stage II) and 1.1 µg/ml (stage III). Each time the new effect-site concentration was achieved, a 5 minute steady state period was maintained.

Learning, delayed recall and delayed recognition evaluation was adapted to the pre-anaesthetic setting using a French version of the eight-word test [15]. This test included three parts (fig. 1).

– *First part (learning);* oral presentation of an eight-word list with immediate recall after each presentation. This was done three times in a standardised way (1 word/second) at stage I (baseline), stage II, and stage III. At each stage, a different eight-word list was presented and the order was balanced in both groups. Thus, during induction of anaesthesia, three lists containing a total of 24 words were presented to each patient.
– *Second part (delayed recall);* after 24 hours, a delayed recall of the three eight-word lists from the first part (total, 24 words) was performed. Patients were asked to repeat all the words that they could remember during a 150-second period.
– *Third part (delayed recognition);* additionally, after 24 hours and immediately after the delayed recall task, a delayed recognition test was performed. The patient had to recognise target words among 48 words that were presented orally. The 48 words were composed of the 24 words that were used in the first part ("targets") and 24 "distracters" that are semantically matched to the targets for category and lexical frequency according to validated lexical databases [16]. Subjects were asked to answer with "yes" if the word was among the 24 targets (hits) or with "no" if the word was a distracter (correct rejections).

Analyses

We tested for normal distribution of patients' performances using the Shapiro W test. For non-normal distribution, median values were reported and comparisons were done with a non-parametric Mann-Whitney test. For normal distribution, we compared memory performance through repeated measure ANOVA, with smoking status as an in-between subject factor and anaesthesia stages as a within subject factor. We also computed a "recognition discriminability index" *d'*, which takes into account the number of correct hits and false alarms, by calculating *d'* under the standard signal detection assumptions as *z* (hits ratio) – *z* (false alarms ratio) [17].

For learning, the *p* level was fixed at 0.05 for significance. Since for delayed performance two variables were analysed (delayed recall and recognition discriminability), the *p*-level for significance was Bonferroni-corrected at $p < 0.025$.

Results

Patient characteristics and clinical data

Data from 24 smokers and 25 non-smokers were analysed. One smoker received pre-medication with a benzodiazepine and was therefore excluded from the analysis. Groups were matched for age (smokers, mean ± SD 40.5 ± 7.1 years; non-smokers, 39.7 ± 13.1 years), weight (smokers, 70 ± 6 kg; non-smokers, 70 ± 3 kg), height (smokers, 170 ± 2 cm; non-smokers, 170 ± 3 cm), gender (smokers, 33% females; non-smokers, 36% females), and educational level (smokers, 2.13 ± 0.54, non-smokers, 2 ± 0.58, ns). Average surgical time was 84 ± 22 min for smokers and 94 ± 33 min for non-smokers. Propofol doses were 902 ± 153 mg (range, 560 to 1180) for smokers and were 871 ± 233 mg (range, 270 to 1200) for non-smokers. Cumulative sufentanil doses were 34.6 ± 5.1 µg (25 to 45 µg) for smokers and were 37 ± 7.36 µg (25 to 55 µg) for non-smokers.

In smokers, average cigarette consumption was 20 ± 3.2 packs per year, and the median time of pre-operative smoking abstinence was 3 hours (range, 2 to 9). Average plasma concentration of nicotine was 36.5 ± 6.2 ng/ml, and for cotinine was 223 ± 35 ng/ml.

Cognitive data

First part (learning)

The distribution of data did not meet the criteria for normal distribution. Non-parametric comparisons showed that total learning performance was equal in both groups: smokers learned a median of 22 words out of 24 and non-smokers learned a median of 21 ($p = 0.58$) (table 1). Stage III, but not stage I or II, was associated with a decreased learning performance in both groups. Post-hoc comparisons showed no differences between groups for stage I ($p = 0.44$), stage II ($p = 0.66$), and stage III ($p = 0.48$).

Second part (delayed recall)

The distribution of data did not meet the criteria for normal distribution. Total recall performance was equal in both groups: across all trials (three lists, 24 stimuli), smokers recalled a median of six words (range, 3 to 10) and non-smokers a median of seven words (range, 1 to 22) ($p = 0.57$) (table 2). Post-hoc comparison showed no differences between groups for stage I ($p = 0.9$), stage II ($p = 0.1$), and stage III ($p = 0.7$). There was, however, a stage effect; words in stage II and III were less recalled than words in stage I.

Third part (delayed recognition)

Recognition performances scores fitted normal distribution. There was no difference (table 3) in hits (smokers, 15.6 ± 4.9; non-smokers, 15.8 ± 4.6 words; $p = <0.46$). Recognition discriminability indexes were, however, higher in non-smokers ($p = 0.019$). Post-hoc analyses revealed a higher number of false recognitions (false alarms) in smokers (4.7 ± 3.9 words) compared with non-smokers (2.4 ± 2.9 words) ($p = 0.029$). There was no group effect (DF = 1, F = 0.56, $p <0.46$). However, there was a stage effect; words in stages II and III were less recognised than words in stage I. There was no interaction between groups and stages (DF = 94, F = 1.39, $p <0.25$), suggesting that smoking did not modify the recognition abilities across sedation stages.

Discussion

The present paper confirms the strong decrease of verbal encoding and retrieval abilities in patients receiving propofol for sedation [18], and provides new information about the impact of chronic smoking on propofol-induced amnesia. As expected, increasing propofol decreased learning performances in all patients. However, when both groups were directly compared we did not observe any difference between smokers and non-smokers in learning performances, neither at baseline (stage 1) nor in both increasing stages of propofol induction (stage II and III). Moreover, delayed recall 24 hours after learning was similar in both groups, independent of the anaesthesia stage in which the words were learned. Finally, delayed recognition of these learned words was similar in both smokers and non-smokers. Thus, results point to similar memory abilities in smokers as in non-smokers, indicate that explicit learning is affected equally by propofol sedation in both groups and suggest that chronic smoking does not have a clinically relevant impact on explicit amnesia induced by propofol.

A classical word-learning task such as the one used here, with encoding, storing and retrieving and recognising information is a way to test memories sensitive to propofol, which are those accessed by consciousness and contain contextual information such as when and where they

Table 1
Respective learning performance (LP) in the three stages of propofol anaesthesia. Stage I: propofol effect-site concentration, 0.0 µg/ml (baseline); Stage II: propofol effect-site concentration, 0.7 µg/ml; Stage III: propofol effect-site concentration, 1.1 µg/ml. Maximum is 8 words for each stage and 24 words for total learning. Data are given in median value (minimum; maximum).

	LP in Stage I	P in Stage II	P in Stage III	Total learning
Smokers	8 (5.8)	8 (4.8)	6 (1.8)	22 (13.24)
Non-smokers	8 (5.8)	8 (5.8)	6 (0.8)	21 (14.24)

Table 2
Delayed recall (DR) 24 hours after propofol anaesthesia in smokers and non-smokers. Stage I: propofol effect-site concentration, 0.0 µg/ml (baseline); Stage II: propofol effect-site concentration, 0.7 µg/ml; Stage III: propofol effect-site concentration, 1.1 µg/ml. Data are given in median value (minimum; maximum).

	DR from Stage I	DR from Stage II	DR from Stage III	Total DR
Smokers	5 (8.2)	0.5 (4.0)	0 (2.0)	7 (24.13)
Non-smokers	6 (8.1)	1 (7.0)	0 (7.0)	7 (10.3)

Table 3
Delayed recognition (number of Hits = H) 24 hours after propofol anaesthesia in smokers and non-smokers. Stage I: propofol effect-site concentration, 0.0 µg/ml (baseline); Stage II: propofol effect-site concentration, 0.7 µg/ml; Stage III: propofol effect-site concentration, 1.1 µg/ml. *d'* corresponds to the coefficient of memory discriminability. Data are given in mean value (SD).

	From Stage I	From Stage II	From Stage III	Total HIts	*d'*	False alarm
Smokers	7.3 (1.7)	5.1 (2.2)	3.2 (1.9)	15.6 (4.8)	1.9 (0.6)	4.7 (3.9)
Non-smokers	7.2 (1.6)	5.7 (2.2)	2.8 (2)	15.8 (4.5)	2.8 (1.5)	2.4 (2.9)

occurred [10]. Encoding and retrieval requires activation of episodic memory networks, which includes medial temporal structures such as hippocampus and Papez's circuit. Chronic exposure to nicotine seems to modulate receptor activity in other structures, such as motor [18], frontal [19], cortex, thalamus and putamen [20]. One explanation for the absence of interaction on learning between smoking and different levels of propofol serum could be that chronic smoking and propofol involve different memory systems; propofol influencing episodic memory [21] and nicotine working memory [6]. Another explanation is that the effect of propofol on episodic memory may be not specific [22]. Independent of the final explanation and taken together, our data suggest a certain independence between effects of chronic nicotine intake and propofol-induced modulation of GABA-ergic transmission. Furthermore, absence of an interaction in learning capacity between smokers and non-smokers and between sedation stages is an argument against a direct propofol-related modulation of the activity of nicotinic receptors.

We have, however, found a marginal difference in recognition discriminability between both groups, with smokers making false alarms slightly more often than non-smokers. These results must not necessarily be considered as an effect of propofol. In fact, we cannot discriminate between an effect of chronic smoking on recognition or a more general impact of chronic nicotine intake itself on memory monitorings [23] or attention or on small subclinical cerebrovascular alterations [31]. A suitable explanation is, as the data suggest, that chronic smoking is associated with a subtle cognitive decrease, even in young smokers, implicating executive functions and memory [3]. Since our study was centred on the effect of propofol on memory in smokers, we did not control for baseline executive factors. Finally, we cannot ignore the role of addiction itself, since the neuropsychological observations of addiction have particularly pointed to deficits in inhibitory control [25, 26], which could explain an increased tendency for false recognition.

In conclusion, otherwise healthy, chronic smokers undergoing propofol-based anaesthesia seem to have the same changes in episodic memory as with matched, non-smoking controls, except for a marginal decrease of recognition discrimination abilities. Anaesthesia, itself, does not interact with memory abilities in chronic smokers.

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