SMOKING-INDUCED ALTERATIONS IN BRAIN ELECTRICAL ACTIVITY: NORMALIZATION OR ENHANCEMENT? V. Knott, Dept. of Psychiatry, University of Ottawa and Institute of Mental Health Research/Royal Ottawa Hospital, Ottawa, Ontario, Canada, K1Z 7K4.

One of the attractions of cigarette smoking may lie in nicotine's ability to enhance normal levels of functioning and/or normalize deficient levels of functioning which may characterize transient situational states or enduring maladaptive traits. Brain electrical recordings from the scalp surface provide a non-invasive strategy for examining the impact of smoking on central functions and their relationship to perceptual, cognitive, and emotional processes. Quantitative electroencephalography (QEEG) and event-related potentials (ERPs) collected during passive and task-activated conditions were employed here to examine putative normalizing/enhancing effects of acute smoking in smokers relative to non-smoking non-smokers. Tasks were specifically selected to tap attentional and memory processes, processes which have been previously reported to be affected by smoking and nicotine administration in both normal and pathological populations. Evidence indicates that the ability of smoking to affect brain function is response/task dependent and that evidence for both normalization and enhancement are observed with neuroelectric recordings.

NICOTINE AND COGNITIVE EFFECTS

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The most satisfactory explanations of tobacco smoking have proposed that smokers are influenced by the psychoactive effects of nicotine. Research conducted at the HPRU suggests that improvements in human cognition and psychomotor performance after the administration of nicotine may be central to the habitual use of tobacco. Investigations into the effects of nicotine on critical flicker fusion threshold show that where the background level of central nervous system arousal is sub-optimal (particularly among abstinent smokers), nicotine acts as a mild cognitive enhancer; this in turn may be the basis of improved performance found in studies investigating the effects of nicotine on attention, particularly the reduction of the vigilance decrement, and is consistent with a cholinergic mode of action for nicotine. Sensori-motor and memory function are also improved by nicotine, and these effects are found in non-abstinent smokers and non-smokers. This may reflect a different mechanism of action, possibly through the release of dopamine. In the wider context, it appears that smokers may be able to manipulate nicotine intake and other parameters of smoking to control and optimize their cognitive and psychomotor performance. If this is shown to be the case, it could follow that nicotine also has a role in modulating mood and assisting in the amelioration of acute and chronic psychological distress. In conclusion, the psychopharmacological profile of nicotine is one of small, but reproducible, specific positive effects on human cognition and psychomotor performance.

EVIDENCE THAT NICOTINE IS ADDICTIVE. LP. Stolerman and M.J. Jarvis, Section of Behavioural Pharmacology and ICRF Health Behaviour Unit, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

Despite the wide-ranging and authoritative 1988 review by the US Surgeon General, views questioning the addictiveness of nicotine continue to be expressed in some quarters. This lack of complete consensus is not unexpected, since no generally agreed scientific definition of addiction exists. However, several lines of evidence from both the human and animal literature support the view that nicotine is addictive, both according to the scientific criteria commonly applied to other drugs and according to the generally understood meaning of the word. Patterns of use by smokers and the remarkable intractability of the smoking habit point to compulsive use as the norm. Studies in both animal and human subjects have shown that nicotine can function as a reinforcer, albeit under a more limited range of conditions than with some other drugs of abuse. In drug discrimination paradigms there is some cross-generalisation between nicotine on the one hand, and amphetamine and cocaine on the other. Both tolerance and sensitization to effects of nicotine can occur, under different circumstances. A well-defined nicotine withdrawal syndrome has been delineated, which is alleviated by nicotine replacement. Nicotine replacement also enhances outcomes in smoking cessation, roughly doubling success rates. In total the evidence clearly identifies nicotine as a powerful drug of addiction, comparable to heroin, cocaine and alcohol. Addiction to each of these drugs has some unique features, and nicotine is no exception; enhancements of cognitive function are not incompatible with addictiveness but rather, they may constitute one of the mechanisms that sustain it. Thus, the notion that nicotine is 'habituating' but not addicting may be consigned to the archives of history.
SELF-ADMINISTERED NICOTINE ACTS THROUGH THE VENTRAL TegmentAL AREA - IMPLICATIONS FOR DRUG REINFORCEMENT MECHANISMS. William A. Corrigall. Addiction Research Foundation and Dept. of Physiology, University of Toronto, Toronto, ONT, Canada MSS 2S1.

Self-administration of nicotine depends on dopaminergic processes, and in particular on the mesolimbic dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens. We have begun to investigate how this interaction occurs. To determine the site of nicotine's action within this system, we have used the nicotinic antagonist dihydoro-ß-erythroidine (DHßE). Focal administration of DHßE into the nucleus accumbens does not alter nicotine self-administration, but microinfusions of the antagonist within the VTA produce a dose-related decrease in self-administration behavior. Similar intra-VTA infusions of the antagonist do not affect motor output, and do not change operant behavior maintained by food, or intravenous self-administration of cocaine. These observations show that self-administered nicotine acts within the VTA to sustain voluntary drug-seeking behavior. In addition, the findings imply that cholinergic mechanisms may influence dopaminergic reinforcement processes in the VTA. The absence of an effect of DHßE on reinforced behavior maintained by food or intravenous cocaine suggests that a tonically-active nicotinic input is not involved in reinforcement. Not surprisingly, muscarinic central nicotinic receptors are desensitised by chronic nicotine. The primary objective of the present study was to establish the nicotine concentrations which caused desensitisation of mesolimbic DA responses to the drug. Osmotic minipumps were used to constantly infuse nicotine or saline for 14 days. In addition the rats were given 5 daily sc injections of saline or nicotine prior to the test day. Microdialysis studies, performed on day 14 showed that, in animals infused with saline, 5 daily sc injections of nicotine increased (P<0.05) the peak DA overflow in the NAc (measured as percent of baseline levels) evoked by an injection of nicotine from 113±21 to 236±81 %. The enhanced responses were abolished in animals constantly infused with nicotine at doses of 4 and 1mg/kg/day and attenuated in animals infused with 0.25mg/kg/day. These infusions yielded plasma nicotine levels of 113±21, 24±5 and 9±4ng/ml respectively. These and other supporting data suggest that the receptors which mediate the stimulatory effects of nicotine on mesolimbic DA neurones are desensitised by nicotine levels commonly found in the plasma of tobacco smokers and imply that tobacco smoking may not invariably result in stimulation of mesolimbic DA neurones.

This study was supported by Forschungsrat Rauchen und Gesundheit and The Wellcome Trust

DESENSITISATION OF THE STIMULATORY EFFECTS OF NICOTINE ON DOPAMINE SECRETION IN THE MESOLIMBIC SYSTEM OF THE RAT. D.J.K. Balfour and M.E.M. Benwell Dept of Pharmacology, University Medical School, Ninewells Hospital, Dundee, DD1 9SY Scotland.

It has been suggested that stimulation of mesolimbic dopamine (DA)-secreting neurones is an important factor in the development of nicotine dependence. However, there is evidence that many central nicotinic receptors are desensitised by chronic nicotine. The primary objective of the present study was to establish which nicotine concentrations caused desensitisation of mesolimbic DA responses to the drug. Osmotic minipumps were used to constantly infuse nicotine or saline for 14 days. In addition the rats were given 5 daily sc injections of saline or nicotine prior to the test day. Microdialysis studies, performed on day 14 showed that, in animals infused with saline, 5 daily sc injections of nicotine increased (P<0.05) the peak DA overflow in the NAc (measured as percent of baseline levels) evoked by an injection of nicotine from 113±21 to 236±81 %. The enhanced responses were abolished in animals constantly infused with nicotine at doses of 4 and 1mg/kg/day and attenuated in animals infused with 0.25mg/kg/day. These infusions yielded plasma nicotine levels of 113±21, 24±5 and 9±4ng/ml respectively. These and other supporting data suggest that the receptors which mediate the stimulatory effects of nicotine on mesolimbic DA neurones are desensitised by nicotine levels commonly found in the plasma of tobacco smokers and imply that tobacco smoking may not invariably result in stimulation of mesolimbic DA neurones.

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MECHANISMS OF ACUTE AND CHRONIC TOLERANCE TO THE BEHAVIORAL EFFECTS OF NICOTINE. J.A. Rosecrans, J.R. James, L.D. Karan. Dept. Pharmacology & Toxicology and Division of Substance Abuse Medicine, Va. Commonwealth Univ., Richmond, VA 23298, USA.

Research conducted in this laboratory over the last 25 years has focused on central mechanisms of nicotine action using a two-lever operant drug-induced Discriminative Stimulus (DS) paradigm. The DS procedure relies on the ability of an experimental subject (rat or human) to be able to detect nicotine from vehicle in order to receive a positive reward. This paradigm is especially interesting since rats do not readily develop tolerance to its DS effects even though rats exhibit pharmacological/behavioral tolerance to nicotine-induced (0.4-0.8 mg/kg, s.c.) disruption of operant behavior; Fixed Ratio (FR) or Variable Interval (VI) schedules of reinforcement. While rats trained to detect nicotine (DS) do appear to develop tolerance to its disruptive effects, recent work has also shown that a select population of rats are capable of exhibiting acute tolerance to the nicotine DS. Experiments were conducted utilizing drug discrimination and operant disruption paradigms in order to learn more about these divergent effects. The results of this work suggests that nicotine-induced tolerance (Acute or Chronic) is contingent on the ability nicotine to induce a desensitization of select central nicotinic-acetylcholinergic-receptors (nAChRs). (This research was supported by a generous grant from the German Research Council on Smoking and Health, Berlin, Germany).