Creatures of habit

ANIMALS IN RECREATIONAL DRUG RESEARCH

A REPORT BY THE BUAV

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Established in 1898, the British Union for the Abolition of Vivisection (BUAV) is Europe’s leading anti-vivisection campaigning organisation. The BUAV is dedicated to using all peaceful means possible to end animal experiments, both nationally and internationally. We combine legal and scientific expertise, media liaison, public campaigning, undercover investigations and political lobbying in order to work effectively for an end to animal experiments and their replacement with modern and humane alternatives. The BUAV chairs the European Coalition to End Animal Experiments (ECEAE), in which it works with animal groups across Europe to co-ordinate campaigning initiatives and ensure that laboratory animals are high on the European political agenda.

The BUAV

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Report summary

Ecstasy, cocaine, cannabis and speed are commonly referred to as ‘recreational drugs’. They cause well known, sometimes serious, physical and mental changes in humans. For this reason such drugs are already controlled by the government to protect public health and safety.

Despite this, nearly 200 studies into the potential harmful effects of recreational drugs on animals were published in the UK alone since the year 2000. This report features twelve examples of recent animal studies, mostly from the UK. They catalogue a range of bizarre, abusive, invasive, repetitive, redundant and even illegal experiments. Experiments include animals being subjected to electric shocks, loud noise, isolation, food deprivation, repeated abdominal injections, implantation of devices and brain surgery.

The usefulness of these studies in advancing our understanding of the harmful effects of these drugs in humans is highly questionable at very best. It has even been questioned by some of the researchers themselves. Differences in anatomy (such as the presence of fur), physiology (differences in metabolism), experience (animals don’t take drugs) and routes of administration (these drugs are not usually injected by users) mean that animals are poor models of the human response. Non-animal methods to discover information of direct relevance to the human situation—particularly studies of current and past recreational drug users—are possible, of demonstrable value and are being conducted at the same time as the animal tests.

Under current UK legislation, experimental projects involving animals should only be licensed when no other alternative exists and after a full analysis of the costs and benefits of the research. This report makes it clear that neither regulators nor researchers are adhering to their own ‘strict guidelines’. Recreational drugs are ‘luxury’ items, used voluntarily (and illegally) by human beings. Any health consequences of their use are entirely avoidable and there is thus no ethical justification for harming animals in these tests. The government already refuses to issue licences for animal tests on other non-essential products such as tobacco, alcohol, weapons and cosmetics. The BUAV therefore calls on the government to extend this ban to include experiments relating to recreational drug use.

The public are funding much of this research through government support of universities and/or Medical Research Council grants and centres (indicated in the text by i). These are funds that would be better spent on relevant, ethical human volunteer research, improving drug rehabilitation centres for those individuals struggling with their addictions, providing information resources to prevent drug abuse and supporting facilities for families living with the consequences of drug abuse.
Introduction

Recreational drug use refers to the taking of psychoactive drugs for recreational purposes rather than for work, medical or spiritual purposes. Common recreational drugs include ecstasy, cocaine, cannabis and amphetamines. Although illegal to produce and supply, and despite awareness of their associated health risks, such drugs are still used heavily in the UK. The main problem facing society is the control and prevention of the use of these drugs rather than obtaining detailed information about their physiological effects.

Animals, however, continue to be used in the UK and abroad to investigate the harmful effects of these drugs. The UK government already refuses to licence experiments on animals for safety testing of other non-essential products such as cosmetics, offensive weapons, tobacco and alcohol. Given that recreational drugs are also non-essential and more importantly, taken illegally, the BUAV calls for this ban to be extended. Under current UK law, researchers are expected to show clear justification for their use of animals, demonstrating that the cost to the animal is lower than the benefit to be gained for humans and that there are no useful alternatives. This report shows using a series of examples that human volunteers studies are entirely possible, are being used at the same time as animal studies and that neither researchers nor regulators are fully examining the cost: benefit ratio of their work.

Consistent findings of this report include:

Researchers resort to animals to either ‘prove’ principles or investigate the mechanisms of action of drugs in relation to brain neurotransmitters or other drugs. Animals are often housed individually or denied normal behaviours; social contact, exploration and restricted amounts of food after testing sessions. The rats were therefore denied the opportunity to perform a range of work comes from the Department of Experimental Psychology, University of Cambridge, UK. These included experiments to compare the effects against other drugs (University of Birmingham) and to evaluate its effects on processing sensory information (University of Sheffield). The latter involved invasive brain experiments conducted under anaesthesia. Several studies also used cocaine as a model of human drug addiction (Universities of Sussex, Dundee and Cardiff). A large body of work comes from the Department of Experimental Biology at the University of Cambridge. Two of their studies on the effects of withdrawal from cocaine and drug seeking are reviewed below.

1 Drug-seeking rats


Location: Department of Experimental Psychology, University of Cambridge, UK.

Rats were used to investigate the progression from casual drug use to compulsive – the kind that characterises drug abusers. Rats were trained to press levers in return for a dose of cocaine delivered directly into their blood stream via implanted catheters in their necks. Rats who had a longer period of this exposure were less likely to stop ‘requesting’ cocaine than un-addicted rats, even when they had been conditioned to associate cocaine with receiving an electrical shock to their feet.

Methods

21 male rats were housed individually and only given restricted amounts of food after testing sessions. The rats were therefore denied the opportunity to perform a range of normal behaviours; social contact, exploration and foraging for food. Individual housing in particular is associated with increased stress and abnormal behaviours.

Rats were then anaesthetised and a catheter (tube) inserted into their jugular vein. This tube extended out and was held in place by being stitched to the rat’s back. No mention was made of post-operative pain relief. They were then trained in small ‘operant’ boxes to press levers, which administered a dose of cocaine remotely through the tubing directly into their jugular vein. As soon as the rats were trained they were placed into another chamber and given ten electric shocks to their feet. They were ‘conditioned’ to associate a loud sound with receiving this foot shock. They were then placed back into the operant boxes and the loud sound made when the ‘drug-seeking’ levers were extended. No mention was made of post-operative pain relief. They were then trained in small ‘operant’ boxes to press levers, which administered a dose of cocaine remotely through the tubing directly into their jugular vein. 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Cocaine

Cocaine is a drug derived from the leaves of the coca plant. The effects of this plant were well-known to the ancient people of South America, where much of this illegal drug is still imported from. Effects include increased energy, a sense of happiness and confidence and a decrease in appetite. It can be psychologically addictive, cause an increase in heart rate and blood pressure and is associated with an increased risk of heart attacks. It is a Class A drug under the Misuse of Drugs Act 1971; possession can lead to a prison sentence of up to seven years.

Research into the non-therapeutic effects of cocaine using animals still continues. Over 50 different experiments published since 2000 were found originating from UK institutions. These included experiments to compare the effects against other drugs (University of Birmingham) and to evaluate its effects on processing sensory information (University of Sheffield). The latter involved invasive brain experiments conducted under anaesthesia. Several studies also used cocaine as a model of human drug addiction (Universities of Sussex, Dundee and Cardiff). A large body of work comes from the Department of Experimental Biology at the University of Cambridge. Two of their studies on the effects of withdrawal from cocaine and drug seeking are reviewed below.

1 Drug-seeking rats


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Rats were used to investigate the progression from casual drug use to compulsive—the kind that characterises drug abusers. Rats were trained to press levers in return for a dose of cocaine delivered directly into their blood stream...
The rats were then given lengthy sessions of lever-cocaine access in order to mimic drug abuse. These rats were then given the electric shock treatment again and assessed for its effects on their willingness to press the ‘drug-seeking levers’. In order to check that rats on cocaine were not just less fearful, the researchers separately trained the rats to respond fearfully to an electric shock, this time in response to a clicker noise. All the rats similarly froze in fear whenever they heard the clicker noise.

Criticisms
In addition to surgery, this study repeatedly subjected rats to novel, confined areas for behavioural testing and to electric shocks and conditioned fear reactions to other stimuli. No mention was made of efforts to ease the suffering of rats now addicted to cocaine at the end of the study. The effects of withdrawal from cocaine were studied by the same authors (see study 2), possibly using the same rats.

To try to recreate cocaine addition in a small rodent over a period of only 20 sessions of drug use is far too simplistic to be meaningful to the human experience. Reasons for drug use and drug abuse cannot be determined by a simple behavioral model where external factors are kept to a minimum. The researchers concluded that “a prolonged cocaine self-administration history endows drug seeking with an inflexible, compulsive dimension”. In other words, cocaine self-administration history endows drug seeking behavior with an inflexible, compulsive dimension. In other words, it is likely that these side effects would be experienced as unpleasant for the monkeys. No mention of training the monkeys to accept being in the chairs and to associate them with positive things was made. To fail to do this is a clear indicator that the researchers did not appreciate the sensibilities of the monkeys.

Methods
28 adult, male rats were given reduced amounts of food prior to behavioural testing in order to make them more amenable (as study 1). Separately, each rat was placed inside a wooden box and presented with five ‘choice chambers’. A small light was lit randomly inside one of five chambers and the rat was rewarded with a food pellet if it stuck its nose into this area. The researchers wanted to know how withdrawing from cocaine or heroin would affect their ability to correctly identify the illuminated chambers. The rats were trained in these chambers at least once a day for two weeks. Catheters were then surgically implanted into their right jugular veins under anaesthesia (as study 1). The rats were housed individually after this and one week later re-trained in the chamber for another week. They were then trained to ‘self-administer’ cocaine, heroin or salt water by being placed in a box and pressing a lever in return for an intravenous shot of the drug via the catheter. This continued once a day for five days with rats receiving up to 50 shots of cocaine and 25 of heroin per day. The rats were then tested in the choice chamber for seven days during ‘withdrawal’ (i.e. no more drugs) to see how this had affected them. The effects of withdrawal from cocaine in rats previously have included depression and anxiety. The researchers did not report on the welfare and behaviour of the rats as a result of this.

The rats were then allowed to become addicted again, for five days at much higher levels of drug (150 shots of cocaine and 75 of heroin) per day, in five daily sessions. They were then tested again in the choice chamber for another week. Control and heroin rats were kept on reduced food rations for a further month and then retested again in the choice chamber since it became apparent that the rats on heroin were less quick to collect the food reward after withdrawing from heroin and the experimenters wanted to know if this ‘lack of appetite’ would last (it did).

3. Drug withdrawal in monkeys
Location: Departments of Pharmacology and Psychiatry, The University of Texas, USA

Sometimes drug users take other drugs to counteract the unpleasant effects of their drug of choice particularly when they are trying to come off it (withdrawal). In order to assess if cocaine use helped withdrawal from opiate drugs such as heroin, researchers used rhesus monkeys had who been given morphine for a long period of time. Every three days they withdrew the monkeys off morphine and tested to see if other drugs such as cocaine, amphetamine and anti-depressants improved their performance in behaviour tests.
Ecstasy

Ecstasy is known scientifically as 3, 4-methylenedioxymethamphetamine or MDMA. It has psychoactive properties, causing feelings of openness and euphoria. It is the second most widely abused illegal drug in Europe23. Users typically take the drug at clubs or other dance music events, which are very often crowded venues with light shows and loud electronic music.

"In the UK there are around 12-15 deaths a year in persons who have taken MDMA. Given the fact that around 500,000 young persons ingest the drug in a very uncontrolled way every week in this country, these figures do not indicate MDMA to be a particularly toxic compound, regrettable though the death of every young person is"24 (Dr. Richard Green, AstraZeneca, our emphasis).

Given this statement, it is perhaps surprising to find that the use of animals to test the effects of MDMA is on the increase24, with over 20 studies published from UK institutions alone since 2000b, including several from the researcher quoted above. The relevance of these studies has been questioned by researchers at the University of Nottingham: "In recent years a large number of animal studies have been undertaken with little emphasis on how the findings relate to human use of ecstasy or MDMA"31.

Ecstasy

Studies on animals have focused on the potential for MDMA to increase body temperature (hyperthermia) or kill brain cells (neurotoxicity). Repeated studies have shown that MDMA induces hyperthermia in rats, mice and guinea pigs and that this is increased in hot or crowded conditions26-29. However, humans appear to be more resistant to over heating (probably because they do not have fur and do not rely on a tail as a heat loss organ25).

It was suggested over 10 years ago that the rare human fatalities are related to genetic variations among the human population in an enzyme that metabolizes MDMA30, a finding that still appears to hold today30.

Repeated studies have also shown that MDMA causes brain damage in a range of animals, however there have been significant differences in these effects depending on species and strain used25. Due in part to an over-emphasis on animal studies there are difficulties in relating these findings to humans. To quote the researchers themselves: "Although the neurotoxic effects of MDMA in animals are widely accepted, the relevance of the animal data to human MDMA users has been questioned"31.

4. Marble-burying mice


Location: Neuropharmacology Research Group, Leicester School of Pharmacology, De Montfort University, Leicester, UK

When small, novel objects such as marbles are placed into a laboratory mouse’s cage, they often try to immediately bury them. This behaviour is thought to reflect that they are feeling anxious and the researchers in this study wanted to know if MDMA reduced this tendency. They injected mice several times with a neurotoxic dose of MDMA and then counted how many marbles they buried.

Criticisms

This study repeats an earlier study on another three monkeys, using different drugs11. It concluded that humans might be using stimulant drugs like cocaine to combat the effects of withdrawal from other drugs of abuse, especially heroin. This information is already known based on reports from humans18,21. One study asked heroin users to rate the effectiveness of a range of drugs at alleviating opioid withdrawal, including cocaine18. They reported that cocaine was not effective in reducing withdrawal, which suggests that the explanations for poly drug use are more complicated13. Whilst the opinions of drug addicts are subjective, this surely has to be more reliable that that inferred indirectly from a different species under unnatural and stressful circumstances.
Methods

Sixteen mice were repeatedly injected into their abdomens with either a high dose of MDMA, PCA (a type of amphetamine) or salt solution as a control. The dose of MDMA given was expected to cause brain damage because the researchers kept the mice in pairs to prevent them overheating and dying. One week later the mice were killed by cervical dislocation and decapitated. When their brains were examined, a significant decrease in important neurotransmitters was found, as expected, however, the researchers did not report how this might have affected the behaviour and welfare of the mice.

The series of injections were then repeated on another set of mice whose ability to bury marbles placed on the top of their bedding was assessed repeatedly for 40 days. The mice given PCA had to be killed after 28 days “on ethical grounds” because they became very aggressive to each other. Then, another 20 mice were injected with one of a range of drugs (including MDMA, methamphetamine (see below), paroxetine (an antidepressant) and methylphenidate (Ritalin) and their marble-burying and general activity observed in a novel cage. Given that moving animals to a novel cage is also highly stressful and that marble-burying behaviour is thought to imply anxiety, it is likely that these animals were under considerable stress.

Criticisms

This piece of research is typical of a range of studies looking for the effects of MDMA on anxiety and brain damage in rodents. The anti-anxiety (anxiolytic) effects at high doses had already been demonstrated in mice and the brain damaging consequences had already been repeatedly demonstrated by the same authors. The relevance of this research for increasing our understanding of the effect of MDMA on humans can also be questioned because this is a very speculative model of human anxiety. Humans do not, of course, bury objects when stressed and marble burying may not even mean that the mice were feeling anxious. It is also not clear why such an indirect measure of anxiety was used when several controlled studies using human volunteers have already reported that MDMA makes them feel calm and happy.

5. White noise and rats


Location: Institute of Neurological Science, Section of Pharmacology, Catanzaro, Italy

Three-month old rats had electrical implants inserted into their brains and were then placed individually into a small box. Some were injected with MDMA into their abdomens and subjected to white noise at a level of 95dB for over 3 hours. The researchers concluded that MDMA together with loud noise causes brain hyperactivity.

Methods

Thirty rats were anaesthetised and placed into a device to enable the researchers to drill a hole into their skull. Four steel electrodes were inserted into their brains and held in place using screws and special cement. The rats had one week to recover but no mention of post-operative pain relief was mentioned. Each rat was then placed in a sound proof box on its own. Each rat’s head was connected to wires to allow an electroencephalogram (EEG) recording device to record activity in the cortex area of the brain (EEG). The rats remained in the box for four hours, half of them were subjected to white noise at a level of 95dB from two loud speakers positioned 30cm either side of the box for the majority of this time. At 87dB humans must wear ear defenders in the workplace. Half an hour later, the rats were injected into their abdomen with either a high or low dose of MDMA or salt solution. Within three minutes the effects of MDMA ‘became apparent’ which suggests that these rats showed signs of ‘serotonin syndrome’ (see study 6).

Criticsims

The volume and type of noise the rats were exposed to may not be directly comparable to humans, who do not normally listen to white noise and have less sensitive hearing than rats. This concern has been raised by others reporting on the study:

“Since the experiments were in rats, it is hard to work out what the results mean for humans.”

Of greater concern is the finding that these results were already known to the authors who said: “In fact it has been well demonstrated that exposure to MDMA produces in mice long-lasting EEG changes”.

An earlier study had also found that MDMA in conjunction with loud noise was neurotoxic in mice. In fact a study, known by the authors, had already demonstrated brain activity changes in human volunteers that were using MDMA. This was measured non-invasively on the surface of the skull, so it is not clear why rats were needed at all and why they had electrodes implanted into their brains. The fact that MDMA and loud noise increased brain activity in rats is not easy to interpret in terms of the mental health of chronic human drug users. To quote the authors “The mechanisms underlying these differences in the duration of effects of similar treatments remain obscure.” Not surprisingly, they recommended more studies.

6. Behaviour in a maze and polydrug use


Location: Department of Psychology, University of Liverpool

Polydrug use (using more than one type of drug) is common with people who take recreational drugs. This is often used as a reason to use animals because the drug the animal receives can be controlled and its effects evaluated separately. Ironically, because poly drug use is so common in humans, researchers also want to look at the effects of this in this study.

The researchers wanted to see what effects ‘pre-treatment’ with a neurotoxic dose of MDMA would have on rats given a dose of cocaine, alcohol, d-amphetamine or heroin. They used an elevated plus-maze test which is designed to assess anxious behaviour.

Methods

200 male rats were housed on their own. Rats are social animals and the Home Office recommends that they are kept with others. They were injected directly into their abdomens with 3 times with a neurotoxic dose of MDMA or salt solution. All MDMA treated rats showed signs of ‘serotonin syndrome’ – which is characterised by an increase in body temperature, agitation, stereotypy, hyperactivity and muscle rigidity. It is perhaps for this reason that they were kept on their own.

Two weeks later the rats were injected again with a dose of cocaine, heroin, d-amphetamine, ethanol (alcohol), MDMA or saline. Twenty minutes later the rats were tested for anxiety by placing them on an elevated plus-maze. This constitutes a raised platform in the shape of a plus (+). The entire apparatus is approximately 0.5 to 1m off the ground, which tends to make the animals very nervous. Two ends of the platform are covered and anxious animals will immediately hide in these areas. The researchers placed the rats on the maze for five minutes. 15 rats fell off the platform and were discarded from the study since the stress was considered too great to continue. Rats given a second injection of MDMA showed clearly anxious behaviours, whilst, not surprisingly, rats given alcohol showed decreased anxiety. Some of the rats were then decapitated and their brains examined for levels of important neurotransmitters.

Criticisms

This study repeated several others that looked at the effects of MDMA on anxiety using the same elevated plus maze test. They found the same results, but crucially no effect of the neurotoxic dose despite it causing (mild) brain damage. They concluded that the use of the elevated plus maze may not be a reliable model for the detection of neurotoxic effect of MDMA. “Caution should be applied in extrapolating derived results.” This is particularly pertinent since study 4, described above, found that MDMA at a neurotoxic dose reduced anxiety.
Cannabis

Cannabis is produced from parts of the cannabis plant and, in contrast to other recreational drugs, users often smoke the raw plant (grass, marijuana). However its effect may be concentrated by harvesting glands in the plant and compressing them to make resin (hashish). The major active chemical compound in cannabis is delta 9-tetrahydrocannabinol or THC, which has psychoactive properties. Cannabis has been smoked and ingested by people for thousands of years and the side effects are well known - increased mental activity, euphoria, overeating, drowsiness, lack of coordination and sometimes anxiety or paranoia. It is registered as a Class C drug in which possession and dealing are still punishable offences. A number of human population studies have suggested a link between cannabis use and mental illness.

An increasing number of experiments in the UK have focused on looking at the potentially beneficial aspects to taking cannabis including for pain relief. However, at least 17 studies involving animals have been published by UK institutions since 2000 on the non-therapeutic or side effects of cannabis. These have included studies looking at the effects of cannabis and cannabis derivatives on physiology (Universities of Nottingham, Pasley and Aberdeen) and behaviour, including memory and learning (Universities of Strathclyde, Aberdeen and Reading), fear (see below) and overeating (Universities of Reading and Birmingham, see below). Somewhat surprisingly, given the relatively mild effects of cannabis, such studies have involved surgery, implantation of medical devices, food deprivation and exposure to fearful stimuli.

7. Fear response to ultrasound in rats


Location: School of Biomedical Sciences, Queen’s Medical Centre, University of Nottingham, UK

The researchers looked at how cannabis-like chemicals altered the fear response of rats exposed to a blast of ultrasound for three minutes. Rats injected beforehand with the drugs were more likely to freeze than flee and had higher levels of stress-related hormones than control rats. The study was then repeated using rats that had steel implants positioned in their necks for the administration of drugs directly into their brains.

Methods
83 rats were injected twice into their abdomens with cannabinoid type drugs (SR141716A and HU210) or placebo. Thirty minutes later they were placed on their own in a circular box (known as an open-field arena) in which they were videotaped to see how quickly they move and in what way. Some of the rats then received a blast of ultrasound at a level of up to 80dB for three minutes. This caused 85% of the rats to flee in fear. Freezing behaviour and defecation was also observed.

“The ultrasound-induced defence response in rats is considered to be analogous to panic in humans”.

Other researchers had shown (by doing it) that ultrasound at a level of up to 80dB can cause freezing and running, and levels above 90dB can cause running jumping and convulsions. It is not clear why the rats had to be exposed to this stimulus for three minutes which, given their inability to actually escape, would have caused considerable stress.

Immediately after this, the rats were stunned and decapitated and their blood collected to determine levels of corticosterone (a hormone which indicates that the animal was stressed). All rats showed a stress response to just being in the novel arena, but those exposed to ultrasound and had received the drugs were more severely affected. The next experiment involved 28 rats who, under anaesthesia, had a steel cannula (a tube to allow precise delivery of drugs) implanted into their brains. They were then housed on their own for the next week and their fear response to the ultrasound was then assessed, as above. Shockingly, investigation of sections of the rat’s brains found that nearly a quarter of the rats did not receive the drugs in the exact location of their brains and so data from them was discarded.

Criticisms
It is already well known that cannabis can induce anxiety and panic attacks in about 20% of people who use it. The researchers also acknowledge that large numbers of studies on animals have reported conflicting results with regard to the effects of cannabis-type drugs. Their study appears to repeat a similar study by the same researchers, so it is not clear how this study has progressed our understanding of the effects of cannabis on fear in rats, or humans.

8. Ability of rats to negotiate a water maze when stoned


Location: Department of Biomedical Science, University of Aberdeen, UK

Rats were placed in a water maze test to see if cannabis extracts affect their spatial and short-term memory. Rats received injections and then had to remember where a platform was hidden under the water. Not surprisingly, based on its well-known effects in humans, cannabis affected the rats’ ability to remember where the safety platform was.

Method
Ten male rats received a total of 20 injections over the course of the study directly into their abdomens of cannabis extracts rich in THC or cannabidiol, or placebo. They were placed into a water maze test which is supposed to test the ability of the rats to remember locations of objects. A water maze is a round pool of water, 1.5 metres in diameter and 0.5 m deep. A Perspex platform is hidden in a random location just under the surface but the water is made opaque by adding powered milk so the rat cannot see the platform. Although rats don’t dislike swimming, the water maze tests exploits their natural inclination to get out of the water. It takes them some time to find the platform and if their memory is good the next time they are placed in the water they tend to head straight for it. If they cannot find a platform sometimes they circle the perimeter of the pool which is thought to indicate anxiety. Once each day the rats were injected with drugs and placed in the water maze for four trials. The tendency for the drugs to cause catalepsy (rigidity of the body) was also tested each time using the ‘bar test’. This involved placing the rat’s forelimbs over a bar held a few inches off the floor. Cataleptic rats will just hang over the bar because they cannot move. Luckily for the swimming rats, the drugs in this instance did not cause extreme catalepsy.

Criticisms
It is already well established that cannabis has effects on short-term memory in humans. Similar studies have already been repeatedly performed on rats using different behaviour tests or on mice using the water maze test. The researchers defended their need to perform this experiment by saying that many of these studies had used synthetic THC and not cannabis extracts, however studies on humans have found no difference in effects between

d: Pub Med search using terms THC, cannabis, animal, UK then reviewed for actual animal experiments relating to negative side effects.
Amphetamines

Amphetamines are a class of drugs with stimulant properties and include d-amphetamine (speed), methamphetamine (METH), Ritalin used to treat ADHD in children and ecstasy (see above). Effects typically include increased activity and attention and loss of appetite. For these reasons speed has been used in the past to increase performance in workers and as a weight loss pill for women. Now, speed and METH are popular drugs used at clubs and music events in addition to ecstasy. Nonetheless, they remain as Class A and B controlled substances with hefty prisons sentences for possession and dealing.

The acute effects of both speed and METH are well known in humans and following extensive tests (over 100 in the UK since 2000), animals too. METH is known to be toxic and cause death to animals. Other symptoms include aggression and stereotypies (repetitive behaviors indicative of distress and brain damage). The doses given to animals are typically in excess of what humans would use and the relevance of these studies has therefore been questioned. Nonetheless, research into METH and d-amphetamine using animals continues. Recent studies have looked at the effect of amphetamine on behaviour (King’s College London), including behaviour following brain damage ( Universities of St Andrews and Cambridge). Amphetamine also causes hallucinations, psychosis and schizophrenia-like symptoms in monkeys. The similarity between these effects with human schizophrenia in particular has led researchers to use monkeys and other animals dosed with speed as ‘models’ of this disease.

Location: Department of Pharmacology, University of Cambridge, UK

In an unlicensed, and therefore illegal, experiment, nearly 300 mice were injected with a sub-lethal dose of methamphetamine, or salt water, and exposed to silence, white noise or loud music (Bach or the Prodigy) at a level of 95dB. Mice exposed to methamphetamine became hyperactive and performed repetitive stereotypies. However, the loud music intensified the effects of the drug, 75% of the mice had seizures and several died.

Methods

267 mice were injected with either methamphetamine or saline and placed in an ‘open field test’ (see study 7). They were then exposed to normal noise levels or white noise, music by the Prodigy or Bach at a level of 95dB for three hours. At 87dB humans must wear ear defenders in the workplace. Mice given METH became hyperactive and then performed stereotypies – repetitive movements that are associated with distress and/or brain damage. These included repetitive head-bobbing, body shaking, forepaw treading, circling and walking backwards. Those given METH and exposed to loud music performed these stereotypies for more than two hours after being injected. The lead researcher said ‘if you saw how the mice behaved, you wouldn’t want to take methamphetamine’.

10. The Prodigy and Bach causes death in mice


9. Overeating rats


Researchers deprived rats of food in order to test the effect of cannabis-based chemicals on motivation to gain access to food. Not surprisingly, given the abundant evidence in humans and from other studies, they found that rats given the drugs were more persistent in pressing levers for food and when given free access to food, ate more.

Methods

32 male rats were deprived of food throughout the experiment for five out of seven days of the week, with the exception of a small amount after testing. This was done in order to encourage the rats to perform. Although the rats did not lose weight during the experiment, given the absence of anything else to do inside their cages, absence of food deprived them of important enrichment. The rats were trained to press levers in return for food pellets inside small (31cm by 33cm) ‘operant training’ chambers. The number of times they were required to press the lever in order to receive the food was progressively increased until the rats gave up trying. Every two days the rats were given an injection into their abdomens of cannabis-type chemicals (THC or HU210) at increasing concentrations and were then tested in the chambers to see how quickly they gave up trying to gain food. Separately to this, eight rats were injected with the drugs and given free access to food to see how much they would eat.

Criticisms

The researchers basically repeated previous studies that suggested an effect of both THC and HU210 on feeding behaviour, only at different concentrations of these chemicals. Crucially, it is already known that cannabis induces overeating (in humans). To quote the authors themselves; ‘Considerable evidence supports the involvement of endogenous cannabinoids in the regulation of food intake’. In fact, a trial of a drug that blocks cannabis receptors in the brain using overweight human volunteers was already known about four years before this study was published. The relevance of the study is also limited because humans are not usually food deprived when they smoke cannabis and it usually makes them crave sweet food. So it may have been more relevant for humans, and kinder to the rats, to have not deprived them of food but offered them sweet food which they also love.

 synthetics and natural cannabinoids. Given the low doses of THC administered and the high proportion of cannabis users in the UK, is it not entirely possible to assess short-term memory using humans? This would prevent the difficulties in extrapolating information on a completely different species using a behaviour test not related to normal human behaviour. Sadly, for the animals, a study looking at short term memory effects in cannabis users has in fact been done.

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In addition, the majority (75%) of the mice in the loud music groups (80 mice) suffered seizures and 10 mice died. At various time points up to five weeks after the initial experiment, the mice were killed and their brains examined. All the mice given METH had signs of brain damage. Prior to this experiment the researchers had identified the sub-lethal dose by injecting a number of mice with increasing levels of METH until they found the dose at which none died but the next dose up would cause death. Since the toxicity of METH is well known in animals it is not clear why they needed to find this dose. It is highly unlikely that the mice received any pain medication before they died.

**Criticisms**

In the words of the researchers "the toxic potential of METH and its derivatives has been known for many years". Crucially, the finding that loud noise and crowded conditions increased death in rodents given amphetamines was reported over 60 years ago84. Nonetheless, the study can be criticised on a number of other levels. Firstly, noise levels at mouse are usually higher than 95dB, so the study did not accurately reflect the human situation. Secondly, the relevance of playing Prodigy or Bach to mice who do not normally listen to such music is also doubtful, even to the researchers who said "our mice had no option but to be exposed to loud music". They noted that the stress of this may have intensified the drug's effects and stated; "there are caveats as to the risks of taking ecstasy. These authors continue to study the effects of these drugs in monkeys".

**Methods**

Five squirrel monkeys, five baboons and three other monkeys were injected three times with a high dose of MDMA. Four of the animals became immediately unwell and two overheated and died. Significant signs of brain damage were found weeks later when the remaining monkeys were killed. The paper caused uproar in the scientific and popular press regarding the dangerous implications of taking MDMA for humans. However, one year later it had to be retracted when the authors admitted the animals had all accidentally been given METH, which was already known to cause these effects.

**11. Lethal toxicity in primates**


Location: Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, USA

Five squirrel monkeys, five baboons and three other monkeys were injected three times with a high dose of MDMA. Four of the animals became immediately unwell and two overheated and died. Significant signs of brain damage were found weeks later when the remaining monkeys were killed. The paper caused uproar in the scientific and popular press regarding the dangerous implications of taking MDMA for humans. However, one year later it had to be retracted when the authors admitted the animals had all accidentally been given METH, which was already known to cause these effects.

**Methods**

Five squirrel monkeys were injected three times with what was meant to be a potentially brain damaging amount of MDMA. One became unwell and wasn't given the third dose, another quickly began to overheat and died. No mention of trying to intervene in this episode or give pain relief was mentioned. Two weeks later the surviving monkeys and another three that had only been given saline were killed and their brains examined for signs of damage. Extensive damage was found in the experimental monkeys, including significant decreases in levels of important neurotransmitters. They found a decrease in serotonin, which is linked to depression and a decrease in dopamine which is linked to Parkinson's disease. Not convinced by this the researchers continued to perform the same experiment on five baboons (one of whom also died immediately), three other monkeys and three control baboons, all of whom were killed weeks later. Autopsy also revealed signs of extensive brain damage in the treated animals.

**Criticisms**

The researchers concluded that "even individuals who use MDMA on one occasion may be at risk for substantial brain injury". In particular they suggested that the reduction in dopamine levels found in the brain might indicate increased risk of Parkinson's disease, something that was picked up by the popular scientific press1. However, one year later the paper was retracted and a comment printed in the journal explaining that the findings were wrong2. The researchers had accidentally given the animals METH, which is already known to be lethal3. These animals' lives were therefore wasted in a badly controlled and useless experiment but no apology was made for this. Public concern was also falsely raised as to the risks of taking ecstasy. These authors continue to study the effects of these drugs in monkeys4.

**12. Effect of speed on isolation reared rats**


Location: Department of Experimental Psychology, University of Cambridge, UK

Researchers wanted to evaluate the effect of amphetamine on learning in schizophrenic-like rats. To induce a schizophrenia-type syndrome rats were reared in isolation and injected with amphetamine. These rats became hyperactive and showed difficulty in learning, which is typical of young animals that have grown up with no other company. The researchers found that amphetamine caused a greater decrease in levels of serotonin, a neurotransmitter that balances mood, but could not explain why.

**Criticisms**

After a particularly invasive and disturbing experiment the researchers commented that the impairments seen in these rats were different to those shown by children with ADHD or schizophrenia. This suggests that the experiment may not have been as relevant to human conditions as anticipated. They also reported differences with other similar studies using isolation-reared rats and noted that different choice type tests produce different results and should be interpreted with caution.
What are the alternatives to animal tests?

Short term effects

The short-term effects of these drugs are well understood as a consequence of historical experience and controlled studies using humans. Such studies continue using volunteers inside and outside the laboratory. For example, blood samples were obtained from volunteers at a rave and the levels of MDMA were correlated with blood pressure, heart rate and body temperature. Another study looked at the cerebrospinal fluid obtained from willing MDMA users to investigate levels of neurotransmitters. Other studies have used questionnaires to identify patterns of use and behaviour problems such as depression. Hospital records have helped describe the effects of MDMA. A recent review suggested a range of other, entirely possible studies that have not yet been attempted, possibly due to an over-reliance on animal studies. Urine samples can be used to confirm actual drug use.

Long term effects

The long-term effects of these drugs on the human body are less well-understood, but cannot be properly assessed in animals with short lifespans living in highly restricted environments. However, since humans continue to use these drugs regardless of their potentially harmful effects, it is entirely possible to learn from these voluntary drug takers. Studies of the effects of chronic drug use are already being conducted, including behavioural tests to look at the effects of long term drug use on memory and learning. Imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have also been used to look non-invasively at the brains of human volunteers. They can help answer questions relating to addiction, drug craving, interactions between drugs and the effects of drug withdrawal. For example, researchers in the USA used fMRI to look at activation of areas of the brain in heavy cannabis users when performing a spatial memory test. They found that the brains of cannabis users had to work harder to complete the tests. Others have used PET to investigate dopamine levels in the brains of methamphetamine abusers and found evidence of brain damage.

Withdrawal studies

Patients at detox clinics have also provided important information on the effects of withdrawal from various drugs. For example, a study of heroin addicts found that those in receipt of withdrawal medication were less likely to use cocaine than those without. Other studies involving volunteers have shown that withdrawing from cocaine results in impairment of visuospatial tasks and other behavioural problems.

Other methods:

A crucial part in the MDMA story relied on the finding that MDMA was metabolised by an enzyme absent in 5-9% of Caucasians. This data was obtained via in vitro techniques.
Conclusion

Animal studies of recreational drug use can cause substantial harm and suffering to animals yet provide data of negligible relevance to human beings. As recreational drug use is a voluntary (and illegal) activity and relevant, effective and humane non-animal research options are available, the use of animals in this kind of research is ethically insupportable.

Recommendations

■ The Government must cease to licence harmful experiments using animals to investigate the effects of recreational drugs on humans.

■ Public funds would be better spent on the prevention and treatment of drug abuse, via education and health clinics.

■ The scientific community must fully exploit all available non-animal methods in researching the health consequences of recreational drug misuse.

■ Scientific, medical and professional journals should refuse to publish animal studies on the health effects of recreational drug misuse.

■ Psychiatrists, psychologists, drug counsellors and other professionals involved in drug treatment should support the call for a ban on animal studies into recreational drug misuse.

■ Drug users and organisations advocating the legalisation of recreational drugs should express their opposition to animal research on this subject.
References

4. Talk to Frank drug information site www.talktofrank.com

\[\text{http://scienceandresearch.homeoffice.gov.uk/animal-research/animal-testing-faq/}\]


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