Julia K.B. Gjerstad

BSc Biomedical Sciences
Student number: 090033595
Newcastle University
Newcastle-upon-Tyne
United Kingdom
Tel: +44 791 540 17 46
E-mail: j.k.b.gjerstad@ncl.ac.uk

Monash University, Australia
School of Psychology and Psychiatry

Can gabapentin and ketamine reduce the severity of morphine dependence and relapse to drug abuse?

Investigation of drug treatments *in vivo* using intravenous self-administration in the rat

Dr Jillian Broadbear, Gholamreza Sepehri, Plato Mak

Introduction

Morphine is an opioid and an effective analgesic agent used clinically for treating pain. For patients with chronic pain conditions the morphine becomes less effective over time, tolerance is developed and as a consequence, larger doses are required to achieve the analgesic effect.

As tolerance develops, physical dependence as well as psychological dependences occur. As a result, patients suffer from pain despite large doses of morphine. In spite of the well-known problems with opioids such as morphine, they are still the most prescribes analgesic agent for treating chronic pain.

Ketamine is a drug that induces alterations of sensory perception by antagonizing the N-methyl-D-Aspartate (NMDA) receptor. It produces anaesthesia and analgesia and is used clinically but is also a drug of misuse.

Some reports suggest that by inhibiting the NMDA receptors, ketamine can prevent or reverse the cellular changes that lead to morphine dependence and tolerance.

Gabapentin is a drug similar to GABA (the main inhibitory nerve chemical in the brain) and it reduces nervous system activation. It is used for reducing pain and for controlling epileptic seizures.

There are mixed reports whether gabapentin is effective for relieving symptoms of morphine withdrawal, however there is evidence that it reduces morphine-withdrawal-induced hyperalgesia.

Aims

The aims of this study is to evaluate the effectiveness of gabapentin and ketamine for reducing:

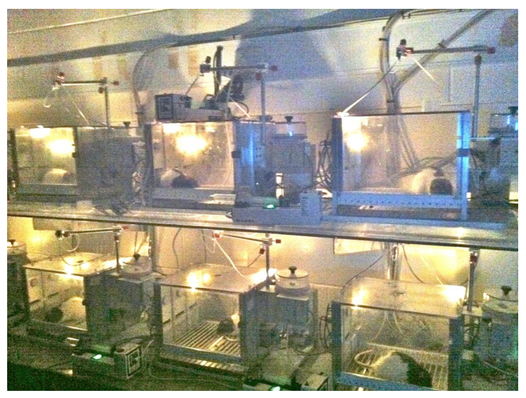
- the amount of morphine the rat learn to self-inject
- the level of physical and psychological dependence the rat will develop after repeated exposure to morphine
- the likelihood that a priming drug injection or stressor will trigger drug-seeking behavior in a formerly morphine-dependent rat that has not had the opportunity to self-inject morphine for an extended period of time.

Methods

Following intravenous catherasation surgery in the jugular vein, the rats commenced their training schedule for morphine self-administration. Self-administration training and testing is performed in operant chambers, each containing three levers with associated stimulus lights. When the rat depresses the active lever infusion of morphine results. The infusion is set to 0.1mg/kg/inf and there is a time-out of 10 seconds.

Once stable self-administration behavior was established (10 to 14 days after acquisition), some rats received naloxone and the level of physical dependence was examined. Subsequently, the rats were put in the operant chambers but no drug was available and extinction could be assessed.

Self-administration will then be reinstated by either a priming morphine injection or a mild stressor (eg restraint stress). During acquisition, withdrawal or following extinction and initiation of relapse, some rats will receive gabapentine (intraperitoneally) or ketamine (via continuous infusion) to determine how these drugs affect morphine self-administration behavior.



Self-administration operant chambers

Results

This is an ongoing study that will continue until the first of the following endpoints are reached: the study aims are completed; the rat doesn't develop/loses the ability to self-administer morphine; the rat no longer has a working venous catheter (in which case a second surgery may take place); or until deteriorating health status of the rat precludes its continued participation in the study.

Further information:

Jillian Broadbear
School of Psychology and Psychiatry, General Office
Room 405, Building 17
Clayton Campus
Monash University
Victoria 3800
Australia
Tel: +61 3 990 53903
E-mail: Jillian.Broadbear@monash.edu

Plato Mak
School of Psychology and Psychiatry, General Office
Room 405, Building 17
Clayton Campus
Monash University
Victoria 3800
Australia
E-mail: plato.mak@monash.edu