Addiction Classics

Rat Park: How a rat paradise changed the narrative of addiction

Suzanne H. Gage1 & Harry R. Sumnall2

1. Department of Psychological Sciences, University of Liverpool, Eleanor Rathbone Building, Liverpool, UK
2. Public Health Institute, Liverpool John Moores University, Tithebarn Street, Liverpool, UK

Word Count: 2633

Conflict of interest: None

Keywords: morphine, biopsychosocial model, ‘Rat Park’, pre-clinical model

‘*Rat Park’ is the name given to a series of studies undertaken in the late 1970s by Bruce K. Alexander and colleagues. They found that rats housed in enriched environments consumed less morphine solution than those in isolated cages, when rats were pre-exposed to morphine, naïve to morphine, and whether they had spent their early life in isolation or in enriched housing. The measured conclusions from the authors at the time have become somewhat lost in translation.*

Introduction

‘Rat Park’ is the name given to a series of studies beginning in the 1970s and led by Bruce K. Alexander in his lab at Simon Fraser University, Vancouver, Canada, where he found that rats living in a social environment were less likely to self-administer oral morphine than those housed in isolation. Alexander and his colleagues interpreted these findings as evidence of the importance of environment in the development and maintenance of addiction, and their neat, intuitive concept has captured public imagination. Popular TED talks about addiction cite the study, and the experiments have even been turned into a comic and animation with millions of views. Organisations campaigning for more progressive drug laws use the paper as a touchstone (along with Robbins’ work on Vietnam veterans, which has also been covered as part of this series (1)) for the importance of consideration of environmental factors in the development and responses to substance use disorders (2).

Behavioural Pharmacology in the 1970s

Alexander has himself written extensively about his motivations for setting up Rat Park. Pre-clinical models of (operant and non-operant) drug self-administration and reinforcement were well-established at the time, in a variety of animals including rodents and non-human primates (3-6). Although there was uncertainty over how well these modelled human addictive behaviour and the conditions under which human drug use occurs (7, 8), knowledge was beginning to emerge of the importance of procedural manipulations and variables such as training techniques, schedule of reinforcement, acute stress, social hierarchy, rearing conditions, and housing of animals (including naturalistic colonies and enriched environments) on drug seeking behaviour (9-14). However, much of this early work was focused on oral intake of alcohol, and Alexander’s programme of work also sought to understand how morphine consumption interfered with the usually socially-orientated rodent colony behaviour that produced social cohesion, reflecting contemporaneous criticisms of the validity of pre-clinical models where drug ingestion was considered a predictable response to experimenter-induced stress (15).

The original 1978 study

The study involved some set-up – the researchers built an L-shaped 8.8m2 enclosure, covered the floor in cedarwood sawdust, and added open boxes, tubes, open-topped cages and a climbing pole. This was thought to provide a semi-naturalistic colony environment with exposure to novel objects and conspecifics that would better model the social environments of rodents. The initial 1978 study (16) consisted of 32 albino Wistar rats. Four females and six males were placed in individual, isolated 18 x 25 x 18cm cages, with no visual contact with neighbouring animals. Ten females and 12 males were placed in Rat Park. For three weeks prior to the experiment all rats had continuous access to both water and a morphine hydrochloride solution, and all consumed water almost exclusively, whether isolated or in Rat Park.

The methods by which water and morphine solution consumption was measured differed depending on housing conditions. Rats in isolation had their water bottles weighed, and the difference recorded as the amount consumed. This was adjusted by comparison to a water bottle attached to an empty cage, as a crude attempt to account for leaking and evaporation. In Rat Park the water bottles were at the end of a clear plastic tube, large enough for one rat only. Each rat had an identifying mark on its back – when they entered the tube a video camera was triggered that recorded which rat had entered. The water bottles released drops individually in to a well below the bottle. A light beam was broken by a rat drinking from the well. When the rat pulled back the light beam reconnected and another drop was released. Counters recorded how many drops had been released – these counters were also recorded by the video camera.

A large amount of data was collected during this study – morphine consumption was measured in three different ways, data was collected on eight ‘forced choice’ days during various stages of the experiment, across the four groups of rats (split by location and sex). After four deaths during the study, there were two isolated females, six isolated males, seven social females and 12 social males. Clearly these are very small group sizes, even for an animal study. The amount of morphine consumed in all periods was highest for the female isolated rats – the group where there were only two animals. Broadly, they found that isolated rats consumed more morphine than rats in Rat Park, and that female rats consumed more morphine than males. Across the four choice-days in the three-day cyclical schedule, isolated rats’ morphine consumption increased, while consumption in Rat Park decreased. However it was not the case, as is sometimes reported, that the rats in Rat Park consumed no morphine.

Alexander and his co-authors’ conclusions were quite measured. They suggested that their findings showed that ‘sex and housing are important variables…’ and that ‘…theories that do not consider these factors run the risk of oversimplification’.

Follow-up studies

After this initial study, the group undertook a further two studies to expand upon their results. The first was a replication of the original study, but using rats with no prior exposure to morphine (17). In this study they gave rats a choice between tap water and a morphine solution that was made progressively more palatable (by increasing sweetness and reducing morphine concentration), in five day increments. Again the results showed that female rats consumed more morphine than male rats, and that isolated rats consumed more than the Rat Park rats. However, these differences were only observed at high-sweetness, low morphine conditions.

A third study investigated whether housing conditions impacted on morphine consumption depending on what age an animal was exposed to the enriched or isolated cages (18). In this study rats were raised either in Rat Park or in isolation, and then when they were 65 days old half were switched. The authors again found that rats in Rat Park consumed less morphine than isolated rats, regardless of where they were raised, although this study found no sex differences. All three studies are described in more detail in Table 1.

There are a number of limitations to the design and reporting of these papers. Perhaps most important is the different method of collecting data for the colony rats versus the isolated rats. If one collects data via different methods for different groups, there is an opportunity for systematic bias to be introduced into a study. For example, if Alexander and his colleagues were underestimating the amount of morphine solution that leaked in the isolated cages, but it was being measured completely accurately in the colony housing, then they would find a difference between the groups even if none were there. However, that they also collected information on water consumption and didn’t see an identical pattern might be some protection against this. Further, the impact of allowing males and females to live together in Rat Park adds another inconsistency between groups – rat pups. It’s not clear from the papers how Alexander and colleagues dealt with any offspring that arose from the mixing of males and females. Pregnancy and weaning impacts on females’ behaviour and nutritional requirements, which could be a source of further bias. Similarly, communal living could lead to competition for resources, which could impact on consumption behaviour related to group dominance dynamics. The small sample size and complex study designs mean there are a large number of possible ways Alexander and colleagues could have analysed their data, and the risk of false positive results are higher.

Nowhere in these original papers do Alexander and his colleagues make the connection between their findings and any implications that they might have for human addiction, or understanding the impact of deprivation or lifestyle on the risk of developing problematic substance use. While contemporaneous researchers were highlighting the importance of environmental and societal influences on human development and substance use (19-21), there was little reference to the biopsychosocial models of addiction that predominate today, and which Rat Park is now oft-cited as evidence for. However, after ending his programme of pre-clinical research, Alexander began to use the findings of Rat Park to develop an adaptive model of drug use, whereby substance use disorders could be considered a response to environmental stressors and chronic distress of any sort (22, 23). This has included a wide range of public lectures and writings, including a popular science book (24).

Replication attempts and contemporaneous studies

Independent attempts to replicate the findings of Rat Park, and expand them to other substances, have produced mixed results. An earlier study had expanded the drugs under investigation to include both morphine and cocaine (12). Their findings were different from Alexander and colleagues’; the Wistar rats in their study showed no difference in morphine consumption whether they had been raised in an enriched environment or an impoverished one. They also found that rats in the enriched environment consumed more cocaine infused water than rats in the impoverished environment. A 1987 study also investigated the impact of environment on cocaine use in rats, this time using intravenous administration after a schedule of lever presses (25). Their results were more in line with Rat Park – isolated rats quickly learnt to press a lever to administer cocaine, while socialised rats did not consistently acquire this behaviour. In 1996 Petrie attempted to replicate Alexander and colleagues’ 1979 study (17), where rats were given increasingly palatable morphine-sucrose solutions over the course of the experiment (26). Petrie ran two experiments, using two different methods to record the data in an attempt to eliminate the potential bias caused by Alexander’s differing measurement techniques between conditions. Across both studies the amount of morphine solution consumed by colony animals was broadly similar to that seen in Rat Park, but the isolated animals in Petrie’s study on average consumed substantially less morphine solution than those in Rat Park. Petrie points out that the strain of Wistar rats had altered since Rat Park, and therefore that the difference found might be due to genetic factors.

Legacy

The Rat Park programme of research was relatively short, and largely in keeping with contemporaneous rodent studies of alcohol. The work of Ellison and colleagues for example, identified variation in rodent self-administration of alcohol to the extent that they were even able to identify rats who preferred drinking in a ‘cocktail hour’ or for a ‘nightcap’ (10). The effects of environmental enrichment on rodent behaviour has been studied further and implicated in behaviours such as reduced stress-induced reinstatement of drug seeking or reduction in naloxone-induced withdrawal. Other studies suggest that the protective effects of environmental enrichment might not be unique to rewarding drugs, and similar findings to Rat Park have been observed with respect to other rodent behaviours, cognitive abilities, stress, and progression of disease (27-29).

Rat Park tells us a lot about animal models of drug reward and self-administration, and for this reason the studies form part of the history of behavioural pharmacology. But in this context Rat Park was not particularly novel, and there have subsequently been more compelling findings describing the complex interactions between individual, social and environmental factors in determining human substance use behaviours (e. g. 30, 31). Rat Park provides a model of one experimental manipulation (housing) on one particular behaviour (morphine self-administration), and so the popular interpretation that the work provided a new understanding of addiction is overstated. Supply, availability, and opportunities for substance use are all important proximal determinants of human substance use, and are not determined by the manipulations of an unseen experimental hand (32), and investigations of the impact of early years adversity highlight that ‘environment’ also includes factors such as poor access to services, social exclusion and the inability of individuals and communities to participate effectively in mainstream social, cultural, and political life (33).

Conclusion

Rat Park is no doubt an important and interesting set of studies, and the core message it suggests - that addiction is more complicated than a biological response to consumption of a drug - is a hugely important one. But that doesn’t mean we shouldn’t read the study itself with a critical eye, or use it to suggest that environment is the only important factor in the development and maintenance of problematic drug use. Differences between rat groups only emerged in very specific conditions – in rats ‘pre-addicted’ to morphine, in the precise concentrations of morphine and sucrose, at certain stages of the experiments. The numbers of rats in each of these studies was extremely small, and the number of comparisons made in each study was high.

Rat Park was broadly aligned with other behavioural pharmacology findings at the time it was conducted, although most rodent drug self-administration studies continue to individually house animals.It highlighted important considerations when designing experimental manipulations, and the influence that environmental factors might have on rat models of addiction. However, whether it is truly an accurate model of human addictive behaviour is more questionable. It is certainly true that numerous studies since Rat Park have shown the importance of environment in influencing human drug use, particularly in early years, but when considering socio-ecological models of health, drug use, drug choice, maintenance and development of problematic use or disorder, these are not simply a product of social environment (or lack thereof), but a complex interaction of individual risk (genetic and environmental) integrated within a larger social system, which are themselves complex and multileveled. However, this is not to construct a ‘straw man’ out of Rat Park - it has endured because advocating policy change requires a ‘good story’ and a simple narrative that has, or should have, at least some basis in evidence (34).

References

1. Hall W, Weier M. Lee Robins' studies of heroin use among US Vietnam veterans. Addiction. 2017;112(1):176-80.

2. Policy TGCoD. The world drug perception problem: Countering prejudices about people who use drugs. 2017.

3. Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology (Berl). 2000;153(1):31-43.

4. Clark R, Schuster CR, Brady JV. Instrumental conditioning of jugular self-infusion in the rhesus monkey. Science. 1961;133(3467):1829-30.

5. Schuster CR, Thompson T. Self administration of and behavioral dependence on drugs. Annu Rev Pharmacol. 1969;9:483-502.

6. Weeks JR. Experimental morphine addiction: method for automatic intravenous injections in unrestrained rats. Science. 1962;138(3537):143-4.

7. Panlilio LV, Goldberg SR. Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction. 2007;102(12):1863-70.

8. Sanchis-Segura C, Spanagel R. Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. Addict Biol. 2006;11(1):2-38.

9. Anisman H, Waller TG. Effects of inescapable shock and shock-produced conflict on self selection of alcohol in rats. Pharmacol Biochem Behav. 1974;2(1):27-33.

10. Ellison G, Daniel F, Zoraster R. Delayed increases in alcohol consumption occur in rat colonies but not in isolated rats after injections of monoamine neurotoxins. Exp Neurol. 1979;65(3):608-15.

11. Heminway DA, Furumoto L. Population density and alcohol consumption in the rat. Q J Stud Alcohol. 1972;33(3):794-9.

12. Hill SY, Powell BJ. Cocaine and morphine self-administration: effects of differential rearing. Pharmacol Biochem Behav. 1976;5(6):701-4.

13. Parker LF, Radow BL. Isolation stress and volitional ethanol consumption in the rat. Physiol Behav. 1974;12(1):1-3.

14. Stolerman IP, Kumar R. Preferences for morphine in rats: validation of an experimental model of dependence. Psychopharmacologia. 1970;17(2):137-50.

15. Khantzian EJ. Opiate addiction: a critique of theory and some implications for treatment. Am J Psychother. 1974;28(1):59-70.

16. Alexander BK, Coambs RB, Hadaway PF. The effect of housing and gender on morphine self-administration in rats. Psychopharmacology (Berl). 1978;58(2):175-9.

17. Hadaway PF, Alexander BK, Coambs RB, Beyerstein B. The effect of housing and gender on preference for morphine-sucrose solutions in rats. Psychopharmacology (Berl). 1979;66(1):87-91.

18. Alexander BK, Beyerstein BL, Hadaway PF, Coambs RB. Effect of early and later colony housing on oral ingestion of morphine in rats. Pharmacol Biochem Behav. 1981;15(4):571-6.

19. Bronfenbrenner U. Toward an Experimental Ecology of Human-Development. Am Psychol. 1977;32(7):513-31.

20. Robins LN, Davis DH, Goodwin DW. Drug use by U.S. Army enlisted men in Vietnam: a follow-up on their return home. Am J Epidemiol. 1974;99(4):235-49.

21. Zinberg N. Drug, Set and Setting: The Basis for Controlled Intoxicant Use. New Haven, Connicticut: Yale University Press; 1984.

22. Alexander BK. The Disease and Adaptive Models of Addiction - a Framework Evaluation. J Drug Issues. 1987;17(1-2):47-66.

23. Alexander BK, Hadaway PF. Opiate Addiction - the Case for an Adaptive Orientation. Psychol Bull. 1982;92(2):367-81.

24. Alexander BK. The globalization of addiction. Oxford: Oxford University Press; 2008.

25. Bozarth MA, Murray A, Wise RA. Influence of housing conditions on the acquisition of intravenous heroin and cocaine self-administration in rats. Pharmacol Biochem Behav. 1989;33(4):903-7.

26. Petrie BF. Environment is not the most important variable in determining oral morphine consumption in Wistar rats. Psychol Rep. 1996;78(2):391-400.

27. Laviola G, Hannan AJ, Macri S, Solinas M, Jaber M. Effects of enriched environment on animal models of neurodegenerative diseases and psychiatric disorders. Neurobiol Dis. 2008;31(2):159-68.

28. Preston KE, Corwin RL, Bader JO, Crimmins SL. Relatively enriched housing conditions delay binge onset but do not attenuate binge size. Physiol Behav. 2018;184:196-204.

29. Toth LA, Kregel K, Leon L, Musch TI. Environmental enrichment of laboratory rodents: the answer depends on the question. Comp Med. 2011;61(4):314-21.

30. Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict Behav. 2012;37(7):747-75.

31. Griffin KW. The epidemiology of substance use among adolescents and young adults: A developmental perspective. Handbook of drug use etiology: Theory, methods and empirical findings. Washington, DC: American Psychological Association; 2010. p. 73-92.

32. MacCoun RJ, Reuter P. Drug war heresies : learning from other vices, times, and places. Cambridge, U.K. ; New York: Cambridge University Press; 2001. xvi, 479 p. p.

33. MacDonald R, Marsh J. Crossing the Rubicon: youth transitions, poverty, drugs and social exclusion. The International journal on drug policy. 2002;13(1):27-38.

34. Cairney P. The politics of evidence-based policy making: Palgrave Macmillan UK; 2016.

Table 1: A description of each of the three Rat Park studies, their methods and their findings

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study | Number of rats in each condition | Key manipulations | Main findings (enriched versus isolated) | Other findings (sex differences) |
| The effect of housing and gender on morphine self-administration in rats (1978) | Isolated group: 4 females, 6 malesEnriched group: 10 females, 12 males | Rats were housed in either individual cages (isolated) or Rat Park (enriched) from weaning. The experiment consisted of 4 parts:*Limited access period*: Access to fluid for 7 hours per day on a 3-day cycle (day 1 choice, day 2/3 morphine HCl only), for 9 cycles*Forced consumption period*: Continuous access to morphine HCl only for 57 days (with 4 choice days throughout)*Nichols cycles period*: 3-day cycle (day 1 no fluid, day 2 only morphine HCl, day 3 only water), for 8 cycles (with 4 choice days throughout)*Abstinence period*: Morphine HCl removed, food and water freely available. Choice days after 2 weeks and 5 weeks morphine abstinence | *Limited access period*: data not presented due to measurement error.*Forced consumption period*: mean morphine consumption was higher for enriched rats (18.6mg morphine HCl/rat) than isolated (13.3mg morphine HCl/rat). Two females in each group died during this period.*Nichols cycle period*: Isolated rats drank less on all days apart from choice days, when they drank more morphine HCl than enriched rats (F=200.9, df 1/69, p<0.001).*Abstinence period*: Isolated rats drank more than social rats (F26.38, df 1/23, p<0.001). One female in the enriched group died during this period. | *Forced consumption period*: During final 2 choice days females drank more morphine HCl than males (F 7.26, df 1/23 p<0.05). No evidence of a housing x sex interaction.*Nichols cycle period*: Females drank more morphine HCl than males (F=67.86, df 1/69, p<0.001). Evidence found of a housing x sex interaction.*Abstinence period*: Females drank more morphine HCl than males (F=36.44, df 1/23, p<0.001). |
| The effect of housing and gender on preference for morphine-sucrose solutions in rats (1979) | Isolated group:9 females9 malesEnriched group:9 females9 males | Rats were housed in either individual cages (isolated) or Rat Park (enriched) from weaning.Rats were given a choice between tap water and the solutions detailed below for 5 days per solution:Water + 5% sucrose (pre-test)0.5mg MHCl/ml water0.5mg MHCl/ml water + 1% sucrose0.5mg MHCl/ml water + 5% sucrose0.5mg MHCl/ml water + 10% sucrose0.3mg MHCl/ml water + 10% sucrose0.15mg MHCl/ml water + 10% sucroseWater + 10% sucrose (post-test) | There was little evidence of an effect of housing at high morphine HCl/low sucrose conditions. When sucrose was 10%, there was evidence for an effect of housing, with isolated rats consuming more morphine HCl solution. The largest difference was found for 0.15mg MHCl/ml water + 10% sucrose condition. | Sex differences were inconsistent.At 0.5mg LHCl/ml water + 1% sucrose females drank less than males, 0.3mg MHCl/ml water + 10% sucrose and 0.15mg MHCl/ml water + 10% sucrose this was reversed. |
| Effect of early and later colony housing on oral ingestion of morphine in rats (1981) | Isolated only group:4 females4 malesEnriched only group:4 females4 malesIsolated THEN Enriched group:4 females4 malesEnriched THEN Isolated group:4 females4 males | Rats were housed in either individual cages (isolated) or Rat Park (enriched) from weaning.At 65 days old, half the rats in each condition were switched to the other condition.Rats were given a choice between tap water and the solutions detailed below for 5 days per solution:Water + 10% sucrose0.06mg quinine sulfate/ml water + 10% sucrose (bitter-sweet comparison)1mg MHCl/ml water + 10% sucrose0.5mg MHCl/ml water + 10% sucrose0.3mg MHCl/ml water + 10% sucrose0.15mg MHCl/ml water + 10% sucrose | Rats living in enriched environment at time of testing consumed less morphine HCl than those in isolation, regardless of their early life experience (F=33.64, p<0.0001). There was no evidence that early environment impacted morphine HCl consumption, and weak evidence of an interaction. | The differences seen in housing consumption were broadly driven by differences in the male rats. There was less evidence for differences in female rats, and no difference in consumption across the sexes. |