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The streptozocin model of diabetes induces neuropathic pain, anhedonia and impaired burrowing in rats

Many diabetic patients experience chronic neuropathic pain leading to a reduced quality of life which poses a huge economic burden to the health system and society. There is a dire need to develop more efficacious analgesics as the majority of patients respond poorly to available treatments. The predictive validity of animal models for analgesia may be improved by reinstating specific innate rodent emotional wellbeing behaviours suppressed by pain (e.g. burrowing, sucrose preference). Streptozocin (STZ) given systemically to rats induces rapid and sustained changes that are seen in diabetic patients i.e. hyperglycaemia, polydypsia and frequently neuropathic pain. In this study we investigated whether the development of STZ induced diabetes in rats over 18 days reduces burrowing and sucrose preference (a measure of anhedonia) in line with neuropathic pain (static allodynia) and if these wellbeing behaviours can be improved by the analgesic, pregabalin and/or social paired housing.

This work was conducted in accordance with guidelines established by the Animals (Scientific Procedures) Act 1986 / ASPA Amendment Regulations 2012. Male Wistar rats (325-425g) were administered a single i.p. injection of 65mgkg STZ or 20mM citrate buffer (pH4.5, CTRL). Animals; CTRL (N=16) or STZ (N=18) were pair housed into 5 CTRL/CTRL, 5 mixed STZ/CTRL and 6 STZ/STZ. One STZ/STZ pair was switched to a mixed STZ/CTRL pair at day 1 post injection as one rat developed hypoglycaemia within 24 hours of STZ injection; 17 STZ rats developed hyperglycaemia (30.2 $\pm$ 0.9 mmol/L, $p<0.001$) by day 7. Evoked static allodynia (Von Frey threshold) was evaluated using Dixon's up-down method (1), burrowing behaviour in the home cage measured the amount of pea shingle (2.5kg) displaced from hollow plastic tubes (320 mm long x 100 mm diameter) and preference for 2% sucrose was expressed as a percentage of the total amount of liquid consumed each day.

STZ pairs show significant polydipsia and polyphagia as early as 2 and 7 days post injection. By 3 days post STZ injection diabetic animals develop significant sensory static allodynia (>70% had 68.2 $\pm$ 4.2% change from baseline, $p<0.001$), impaired burrowing (680 $\pm$ 172g, $p<0.001$) and reduced sucrose preference (20$\pm$13%, $p<0.001$) as compared with CTRL group (1650 $\pm$ 149g; 84$\pm$ 2%). Although the impaired burrowing and anhedonia emerge at the same time as the static allodynia in STZ diabetic rats the anhedonia disappears (64$\pm$ 4%, $p>0.05$) and the impaired burrowing deteriorates further (102$\pm$ 38g, $p<0.001$) after 9 days, whilst the static allodynia remains consistent over 18 days. Pregabalin (30mgkg p.o. at 1 and 2 hours post treatment) completely reversed static allodynia (PWT 1 hour, 19$\pm$ 2g, $p<0.001$) but not impaired burrowing (73.1 $\pm$ 52g, $p>0.05$) as compared with vehicle treated rats (PWT 3.1 $\pm$ 0.3g, 86.7 $\pm$ 78.9g) between day 14 and 18 post STZ. Interestingly the early decline (day 3-10) in burrowing in STZ rats in pain is significantly reversed if they burrow in pairs (day 3; 1571 $\pm$159g, day 10; 848 $\pm$ 159g, $p<0.01$), whilst pairing offers no social benefit to CTRL rats burrowing performance ($p>0.05$). Furthermore, social housing of CTRL rats with polydipsic STZ rats in pain alters their nociceptive responses and behaviour leading to hyperglycaemia, demonstrating rodents can recognize pain related responses in conspecifics.

We establish that acute anhedonia and impaired burrowing in STZ diabetic rats may offer an affective sensitive and objective measure of pain and/or diabetes in this model. Furthermore it is clear that social pairing of diabetic rats can have a positive impact on welfare whilst the pairing of control rats with diabetic rats in pain can have a negative impact.

Dixon WJ. (1980) Ann Rev Pharmacol Toxicol. 20, 441-62.