Stimulus properties of drugs and the behavioural pharmacology of pain: in memory of Francis Colpaert

Behavioural Pharmacology 2011, **22**:379–381

Francis Colpaert, who died in 2010 at the tragically early age of 59, was a founder member of the Editorial Board of Behavioural Pharmacology, and was President of the European Behavioural Pharmacology Society at the time when Behavioural Pharmacology was adopted as the official journal of the Society. Francis Colpaert made major scientific contributions in two main areas: the stimulus properties of drugs, as explored through drug discrimination procedures and the phenomenon of state-dependent learning, and the pharmacology of pain, with particular reference to the development of tolerance to the effects of analgesic drugs. On learning of his untimely death, the Editors of Behavioural Pharmacology immediately decided to place earlier plans for the 2011 Special Issue on hold, and instead to focus this Special Issue on these two areas of research.

The Special Issue opens with a tribute to Francis by his long-standing friend and colleague Ian Stolerman, another founder member of both the Editorial Board of Behavioural Pharmacology and the EBPS. The obituary is followed by a further personal tribute that opens a brief review by Bond and Giles of the paradoxical use of drug tolerance to produce chronic effects that are the opposite of those observed acutely. This phenomenon was used to good effect by Colpaert and colleagues to develop a selective high-efficacy 5HT1A agonist as a novel approach to pain control, as described in the following paper by Bardin, which reviews the involvement of serotonergic mechanisms in chronic pain states. Another novel target for pain control, the delta opiate receptor, is surveyed in a detailed review, by Gaveriaux-Ruff and Kieffer, of the novel methods now available for studying this system, and the cellular mechanisms that regulate delta-receptor function.

Two further reviews address aspects of Francis Colpaert's other major research area, the stimulus properties of drugs. Stolerman *et al.* have reviewed the role of training dose in drug discrimination. Their findings suggest that relationships between training dose and the acquisition of stimulus control are quantitatively simple, but qualitatively more complex: they suggest that three-lever procedures may have greater potential to reveal these subtleties. Koek explores the similarities and differences between drug discrimination and state-dependent learning, as revealed by the procedure introduced by Colpaert 25 years ago, in which the same response, reinforcer and reinforcement schedule are used to study both phenomena.

There follow eleven empirical reports of drug discrimination research, the first four of which illustrate the different research methodologies that this procedure supports. One of the principal strategies adopted in drug discrimination research is to ask whether pharmacological agents with known mechanisms of action can modify the discriminative stimulus effects of the training drug. Babalonis *et al.* have used this approach to examine whether the neurosteroid progesterone influences discriminative and other effects of the benzodiazepine triazolam: this study also illustrates a particular strength of the drug discrimination methodology, that it can be applied effectively in different species, including humans. The second major strategy in drug discrimination research is to use generalization from the training drug to other agents to explore the extent of similarity in their effects (a question that is particularly cogent in relation to potential abuse liability when the training drug is a known drug of abuse), and also to characterize the neurochemical actions of the training drug. Peet and Baker have used this method to examine, in rats, the similarity to the parent compound of two synthetic derivatives of the kappa-opioid agonist, salvinorin A, as well as generalization to agents acting at different receptor systems. The next paper provides an example of how generalization from a training drug to novel agents can be used in drug discovery programmes to identify potential therapeutic agents: Wiebelhaus *et al.* report that chronic treatment with metabolites of the atypical antipsychotic drugs clozapine and olanzapine causes tolerance to the discriminative stimulus properties of the training drug and also cross-tolerance to the clozapine cue, suggesting a similarity in the mechanisms of action of these agents. A paper by Wessinger *et al.* illustrates a third strategy, research directed towards further development of drug discrimination methods. They report on the ability of pigeons to perform a four-choice discrimination between no-drug, drug A (a mu-opioid), drug B (a kappa-opioid), and their combination, using both fixed ratio and fixed interval schedules.

The next three papers examine aspects of cannabinoid discrimination. Wiley *et al.* report that mice trained to discriminate the exogenous cannabinoid THC failed to generalize to the endogenous cannabinoid analogue

0955-8810 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/FBP.0b013e32834a66b0

methanandamide, and vice versa. Together with a failure of the CB1 antagonist rimonabant to block the methanandamide discrimination (while blocking THC discrimination), these results suggest that the actions of exogenous and endogenous cannabinoids differ in some important respects. Wakley and Craft report on the interactions between opioid and cannabinoid drugs. Methadone disrupted performance in rats trained to discriminate THC, but had no effects on the antinociceptive and motoric effects of THC in the same subjects, suggesting a differential involvement of mu-opioid mechanisms in different behavioural effects of THC. Jarbe *et al.* examined the ability of four cannabinergic indoles (one of which is present in the 'legal high', 'spice') to substitute for THC in THC-trained animals. Differential antagonism of these compounds by rimonabant suggests that they act via two distinct mechanisms. Together, these three papers illustrate the way in which the use of drug discrimination methods has enhanced knowledge of cannabinoid pharmacology.

Another set of papers has used drug discrimination methods to ask questions about the receptor mechanisms underlying the effects of four psychostimulant drugs. Marona-Lewicka and Nichols used drug discrimination to examine the interaction between 5HT and dopamine in the psychostimulant effect of (+)-amphetamine. They report the (+)-amphetamine cue was potentiated by a $5HT_{1A}$ receptor antagonist, an effect previously reported with agonists at $5HT_{2A/2C}$ receptors. Wooters *et al.* studied the ability of a range of glutamate receptor ligands to substitute for or antagonize the methamphetamine cue. They report that AMPA and mGluR5 ligands were ineffective, but the methamphetamine cue was potentiated by NMDA antagonists. Hiranita *et al.* examined the effects of selective sigma-receptor agonists in rats trained to discriminate cocaine. These drugs have previously been shown to be self-administered by rats trained to self-administer cocaine; however, they did not substitute for cocaine in the drug-discrimination assay, suggesting that cocaine-like subjective effects may not be necessary for their self-administration. Finally, Gleason *et al.* report on the receptor mechanisms underlying the discriminative stimulus effects of the dopamine D_1 receptor agonist dihydrexidine. A complex pattern of results suggests that these effects may also involve actions at dopamine $D_{2/3}$ receptors.

In addition to these papers dealing with stimulus properties of drugs, this Special Issue also includes nine empirical studies of pain and antinociception, including three papers each on acute, persistent, and chronic pain states. The three acute papers all deal with aspects of tolerance to the antinociceptive effects of mu-opioid receptor agonists. The first study, by Dykstra *et al.*, used the hot-plate test to examine the involvement of NMDA receptors in tolerance to morphine. Morphine tolerance was unaffected in mice with knock-down of the NR1 subunit of the NMDA receptor, or by a NMDA antagonist, suggesting that that there is no prominent involvement. Morgan and Nicholson used a tail-withdrawal procedure to study the antinociceptive effects of the isomers of methadone, which as a racemic mixture is a potent long-acting analgesic. Although both isomers were effective acutely, when administered chronically d-methadone blocked the development of tolerance to l-methadone, suggesting that d-methadone may act as a partial agonist at the mu-opioid receptor. Tuerke *et al.* used the tail-flick test to examine the paradoxical ability of ultra-low doses of mu-opioid antagonists to potentiate antinociceptive effects of morphine. They report that ultra-low dose naltrexone attenuated the development of tolerance to the antinociceptive effect of morphine but not the cataleptic effect, implying that catalepsy does not contribute to the paradoxical antinociceptive effect of naltrexone and suggesting a potential clinical role for antagonist-agonist combinations in pain control.

Three papers present evidence for novel analgesic agents identified using the formalin model of persistent inflammatory pain. Marinho *et al.* report that a novel tetrahydropyran derivative was effective in formalin and acetic acid pain models in mice, as well as in acute pain tests; the effects were reversed by naloxone and showed cross-tolerance to morphine, suggesting that they were opioid mediated. Boules *et al.* report that neurotensin, which has previously been found to show non-opioid (naloxone-independent) antinociception, acted synergistically with morphine in the formalin test, suggesting that adoption of this drug combination might enable the use of lower doses of morphine to achieve relief from persistent pain. Dolan *et al.* used a novel formalin test in sheep to characterize the involvement of group III metabotropic glutamate receptors: they report antinociceptive effects of a selective mGluR7 agonist, but not a non-selective group III receptor agonist, suggesting a specific role for the mGluR7 receptor.

The final three papers report on potential novel therapeutic agents for chronic pain states. Bagdas *et al.* report that CDP-choline, and its metabolite, choline, produced an antinociceptive effect in neuropathic (chronic constriction injury) and inflammatory (carrageenan) pain models. Pharmacological studies suggest that these effects were mediated primarily by an increase in acetylcholine synthesis and release, and stimulation of nicotinic receptors containing the $\alpha 7$ subunit. Mico *et al.* assessed the effect of milnacipram, a serotonin and noradrenaline reuptake inhibitor previously shown to be effective in a variety of pain states, in a rat model of polyarthritis. Milnacipram was shown to have efficacy similar to that of a non-steroidal anti-inflammatory drug, idomethacin. Finally, Khasabova *et al.* examined the effects of synthetic cannabinoid CB1 and CB2 receptor

agonists in a mouse model of tumour pain. Selective agonists of both receptors had efficacy similar to that of morphine, and they acted synergistically when co-administered. The results suggest a potential role for drugs acting at peripheral cannabinoid receptors in the management of cancer pain.

Francis Colpaert often expressed the view that Behavioural Pharmacology should publish more papers dealing with pain and analgesia. We suppose that he would have enjoyed reading this Special Issue.

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July, 2011