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The role of training dose in drug discrimination: a review

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Abstract

Drug discrimination has been an important technique in behavioural pharmacology for at least 40 years. The characteristics of drug-produced discriminative stimuli are influenced by behavioural and pharmacological variables, including the doses used to establish discriminations. This review covers studies on the effects of varying the training dose of a drug in a search for general principles that are applicable across different drug classes and methodological approaches. With respect to quantitative changes, relationships between training dose and rate of acquisition or magnitude of stimulus control were found for most drug classes. Acquisition accelerated with dose up to a point beyond which drug-induced impairments of performance had a deleterious impact. Sensitivity to the training drug as measured by ED_{50} values typically increased when the training dose was reduced. Qualitative changes were more complex and appeared to fall into three categories: (i) changes in profiles of generalisation between partial and full agonists; (ii) reduced specificity of some discriminations at small training doses and (iii) changes in the relative salience of actions mediated through different neurotransmitter systems or from central and peripheral sites. Three-lever discrimination procedures incorporating 'drug versus drug' or "dose versus dose" contingencies enabled detection of more subtle differences than the simple 'drug versus no drug' approach when applied to the opioid, hallucinogen and barbiturate classes of drugs. These conclusions have implications for the interpretation of data from studies that utilise either within- or between-subject designs for studying the discriminative stimulus effects of drugs.

Keywords

Drug discrimination; review; psychomotor stimulants; ethanol; opioids; nicotine; GABA-mimetics; hallucinogens; cannabinoids

Introduction

Drug discrimination has served as an important technique in behavioural pharmacology for at least 40 years, with applications in drug discovery, behavioural pharmacology and testing for abuse liability. The characteristics of drug-produced discriminative stimuli are not fixed and invariant, but are influenced by behavioural and pharmacological variables. The dose of drug used to establish a discrimination is thought to influence both its qualitative and its quantitative characteristics. Dose selection is therefore critically important in study design; different studies of the same drug may not use the same training dose and may therefore yield varying results. When using drug discrimination procedures in, for example, drug

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discovery or drug abuse research, incomplete knowledge of training dose effects can lead to incorrect assumptions about receptor mechanisms and abuse liability.

For many classes of discriminable drug systematic, within-experiment, studies of the role of training dose have been published and these can be an invaluable guide for planning research. This article reviews such studies in order to identify any general principles that may emerge. Experiments of this type were published from the early 1970s onwards, the first apparently being Cameron and Appel (1973), followed by Hirschhorn and Rosecrans (1974) and Overton (1975). These studies covered lysergic acid diethylamide (LSD), nicotine, dissociative anaesthetics and pentobarbital and they were soon followed by investigations with amphetamines, benzodiazepines, opioids and alcohol.

This review covers the majority of relevant studies deemed to be of adequate quality; systematic variation of training dose within a study is the key criterion for inclusion alongside other standard indicators such as peer-review publication, adequate numbers of subjects, descriptions of methodology, etc. The drug discrimination database, searched with the keyword “training dose varied”, was a major bibliographic source (Meisch et al. 2011). Several previous articles contain useful but less comprehensive reviews on this subject (e.g. Järbe, 1989). The quantitative characteristics of drug discriminations include numbers of training sessions to establish a discrimination, maximum attainable discrimination accuracy, and ED_{50} values when dose-response curves are determined. The ED_{50} value is commonly used as a measure of subjects’ sensitivity to drugs and it is widely believed that lower training doses are associated with lower ED_{50} values; the evidence for this assumption will be assessed. Additionally, training dose may impact upon qualitative aspects of a discrimination, as defined by changes in the drugs to which generalisation occurs, and sensitivity to antagonists. Evidence from studies directly comparing different training doses will be used to assess support for the view that lower training doses lead to reduced pharmacological specificity of the resulting cue. A different perspective is that as training dose is reduced, the relative salience of the different stimulus elements in a complex, drug-produced stimulus changes, leading to increases in generalisation to some drugs and reduced generalisation to others. The concept of drug-induced discriminative stimulus complexes was discussed explicitly in seminal papers by Francis Colpaert (Colpaert et al., 1976a,b) and it underlies much later thinking in the area.

This review aims to consider whether any general principles relating to the impact of training dose can be identified, in terms of similarities of findings across different drug classes, methodological approaches and other variables. It is subdivided into sections covering different drug classes, with the classes studied most intensively with respect to training dose generally appearing before the classes subjected to fewer investigations. The final section aims to draw together the findings from the different drug classes.

Psychomotor stimulants

Cocaine

Rodent and monkey studies utilising within-subjects designs revealed quantitative differences in the cocaine stimulus when fading procedures were used to establish low dose discriminations (Colpaert and Jansen, 1982; Terry et al., 1994; Spealman and Bergman, 1994) but not when training doses were increased (Craft and Stratmann, 1996). ED_{50} valuesdecreased at low doses, often accompanied by decreased specificity. Colpaert and Janssen (1982) reported that as training dose decreased, so too did the slope of the generalisation curve. Between-subjects studies also revealed quantitative differences: typically, sensitivity of discrimination was increased at lower doses, with lower ED_{50} values (Colpaert and Jansen, 1982; Callahan et al., 1992; Kantak et al., 1995, 1999; Schechter,

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1997; Costanza et al., 2001; Wilcox et al., 2001; Quinton et al., 2006). Colpaert and Janssen (1982) reported steeper generalisation gradients at lower doses which mirrored within-subjects comparisons in the same study. However, others have not reported variations in slope with training dose. The study of Colpaert and Janssen (1982) is also noteworthy because it presented direct comparisons of error rates in drug and non-drug training sessions; at certain training doses, the response after cocaine was acquired more rapidly and thus a relatively large proportion of errors occurred in non-drug sessions.

Most studies of qualitative differences between high and low dose cocaine cues have utilised between-subjects designs in rodents. Dopamine-releasing agents generalised fully at all training doses (Schechter, 1997; Cunningham et al., 2006; Quinton et al., 2006). The selective dopamine reuptake inhibitor GBR12909 and dopamine D1 receptor agonists fully generalised at all training doses (Kantak et al., 1995). However, competitive NMDA antagonists substituted for low but not high doses of cocaine (Kantak et al., 1995). Apomorphine, a mixed D1/D2 agonist, substituted more fully at low cocaine doses (Colpaert and Jansen, 1982; Kantak et al. 1995). Conversely, D2 agonists substituted to a greater extent at high doses whereas D2 antagonists and inverse agonists shift the generalisation curve rightwards at both low and high doses (Costanza et al., 2001). Together these studies suggest a divergence of the dopaminergic substrates mediating the stimulus properties of low and high cocaine doses.

In squirrel monkeys, Spealman (1995) reported GBR 12909 substituted for cocaine at low and high doses, selective noradrenaline reuptake inhibitors (SNRI) substituted for the low dose only, while a selective serotonin (5-HT) reuptake inhibitor (SSRI) and noradrenaline α1, α2 and β2 agonists did not substitute at any dose. Pretreatment with an α1 antagonist attenuated cocaine generalisation at both doses and the low-dose cocaine-like effects of the noradrenaline but not the dopamine reuptake inhibitor. Pretreatment with a non-selective α2 and β antagonist did not influence cocaine generalisation at any dose. Pretreatment with a low dose of the SNRI talsupram potentiated high and low dose cocaine-like responding after GBR 12909. Together these findings suggest that noradrenaline reuptake and α1 mechanisms play a role in the stimulus effects of cocaine. In line with this hypothesis, agents with noradrenergic activity, including cocaine analogues and modafinil, fully substitute for low but not high cocaine doses in rodents (Wilcox et al., 2001; Cunningham et al., 2006; Dopheide et al., 2007).

Cocaine-trained subjects often generalise partially to opiate agonists: morphine produced additive effects upon drug-lever responding at a low dose of cocaine, an effect thought to be mediated by morphine-induced release of dopamine (Kantak et al. 1999). Kappa selective agonists shifted the low-dose cocaine generalisation curve to the right but did not fully generalise with the cocaine cue, and delta-selective agonists did not generalise with or alter the cocaine cue at any of the training doses used in monkeys (Spealman and Bergman, 1994). Finally, nicotinic agonists fully substitute for both low and high cocaine doses (Cunningham et al., 2006).

Kleven and Koek (1997, 1998) trained rats to discriminate high doses of cocaine from low doses and found that high cocaine doses elicited more accurate responding, i.e. more correct lever-selections. Administration of non-selective β-adrenoceptor antagonists, but not β1 or 5-HT_{1A} antagonists, together with the low dose of cocaine, switched responding from the low to the high dose lever, suggesting a role of a β2 mechanism in the high dose cue. SSRIs and SNRIs also increased high dose responding in combination with the low cocaine dose, indicating a role of 5-HT and noradrenaline in the stimulus effects of high cocaine doses.

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In summary, the discriminative effects of cocaine are influenced both quantitatively and qualitatively by training dose. At low doses, discriminative effects are probably mediated by dopaminergic and noradrenergic systems involving D1, D2 and α2 receptors respectively. At high doses, effects at D2, β2, and 5-HT (but not 5-HT_{1A}) receptors may be more important.

Amphetamines

In humans, amphetamine discrimination was readily acquired (Kollins and Rush, 1999). Stimulus control was significantly better at higher training doses in the sense that vehicle produced more drug lever responding in the low dose group than the high dose group. However, generalisation curves were shifted leftwards at lower doses. Interestingly, there were similar leftward shifts in the dose-response functions for some self-reported subjective effects including drug liking and sociability, but not for others such as euphoria or anxiety, suggesting some dissociation between the discriminative stimulus and subjective effects of amphetamine in humans.

Most studies have utilised between-subjects designs with rodents to study quantitative differences in the stimulus properties of amphetamine as a function of training dose. Some have shown that generalisation curves are steeper at low doses (Stadler et al., 2001) while others have reported steeper curves at high doses (Stolerman and D'Mello, 1981). Overall, the accuracy of discrimination was enhanced at higher doses, yet at lower doses ED_{50} values were often lower, albeit non-significantly, indicating enhanced sensitivity i.e., an ability to discriminate smaller doses of drug from vehicle (Stolerman and D'Mello, 1981; Barrett and Steranka, 1983; Snoddy and Tessel, 1983; Sanger, 1988; Stadler et al., 2001). For example, Stolerman and D'Mello (1981) reported increases in drug-lever responding after 0.06 mg/kg in rats trained with 0.4 mg/kg, while those trained at 1 mg/kg did not show increased drug-lever responding at doses of amphetamine below 0.5 mg/kg.

Cocaine fully substituted for amphetamine and its ED_{50} was lower at low training doses (Stadler et al., 2001; Stolerman and D'Mello, 1981). Para-hydroxyamphetamine, which is highly lipophilic and thus penetrates poorly to the central nervous system, showed greater generalisation at low training doses but conversely, apomorphine substituted more at higher doses (Colpaert et al., 1976c; Stolerman and D'Mello, 1981). Gaiardi et al. (2001) found that dizocilpine, a non-competitive NMDA antagonist, generalised more with a low dose while CGP 43487, a competitive antagonist, did not.

Other findings suggest a role for noradrenergic mechanisms in the stimulus effects of low amphetamine doses. Nisoxetine, a noradrenaline reuptake inhibitor, generalised with the interoceptive effects of a low but not a high training dose of amphetamine in mice, and pretreatment with nisoxetine shifted the low dose generalisation gradient for amphetamine leftwards (Snoddy and Tessel, 1983). In contrast, a study in rats did not report any influence of α2 antagonists upon the discriminative effects of high or low amphetamine doses (Sanger, 1988). Thus, the differential involvement of α1 and β adrenoceptors as a function of training dose remains to be clarified in rodents.

In summary, both human and animal studies illustrate quantitative differences in the stimulus effects of high and low training doses of amphetamine. At low doses stimulus control was weaker but subjects exhibited greater sensitivity to small doses of amphetamine. There is limited evidence for qualitative variation in the discriminative stimulus properties of low and high amphetamine doses, although suggestions that peripheral stimulation may be more important at low doses warrant further investigation.

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Caffeine

Human studies demonstrate that caffeine is readily discriminated from placebo at doses as low as 10 mg and even at 1.8 mg in some individuals (Griffiths et al., 1990; Mumford et al., 1994). These studies show that sensitivity to the stimulus effects of caffeine is positively correlated with the number and magnitude of self-reported subjective effects, indicating a functional relationship between these behavioural properties of caffeine. Findings also suggest that low caffeine doses are discriminated based upon the alerting and positive mood effects.

Studies with rodents demonstrate that the interoceptive effectsof caffeine vary quantitatively with training dose (Holtzman, 1986; Mumford and Holtzman, 1991; Powell et al., 1999). At high training doses, discrimination was acquired faster and the generalisation gradient shift rightward. The stimulus properties of caffeine vary qualitatively with dose. Other stimulant drugs, including cocaine, amphetamine, methylphenidate and ephedrine substituted more fully at lower doses, as did other methylxanthines (Holtzman, 1986; Mumford and Holtzman, 1991). The low-dose cue partially generalised to dopamine agonists and may be attenuated by α-noradrenaline or dopamine antagonists, by adenosine analogues, and diverse behavioural depressants. In contrast, the high-dose caffeine cue was harder to characterise; the only agent that fully generalised was theophylline (Mumford and Holtzman, 1991) and dopamine antagonists did not block caffeine (Powell et al., 1999). Agents which produce anxiety-like behaviours in animals, such as benzodiazepine inverse agonists, and the adrenoceptor antagonist yohimbine did not generalise at high training doses. The NMDA antagonist phencyclidine (PCP) also did not generalise.

In summary, there is close agreement between the results of human and animal studies which demonstrate that the caffeine cue varies quantitatively and qualitatively with training dose. At low doses, discrimination appears to be based upon states of alertness or arousal mediated by adrenergic and dopaminergic systems. However, the substrates mediating discrimination at high doses remain unclear.

Opioids

A study in human subjects trained to discriminate progressively lower doses of the μ-opioid agonist hydromorphone, considered together with data from animal studies on buprenorphine, indicated that the progressive reduction of the training dose most likely enhanced discrimination sensitivity (Preston and Bigelow, 1998). A firmer conclusion was not possible, in part because dose-response curves for hydromorphone at the different training doses were not determined. Variation in the training dose of opioids has been examined more extensively in rats and pigeons.

Overton and Batta (1979) used a T-maze procedure to train rats at several doses of various opioids; the numbers of sessions to criterion was inversely related to training dose. Investigations using two-lever procedures showed that ED_{50} values for full opioid agonists decreased at lower training doses, both in between-group studies (Shannon and Holtzman, 1979; Colpaert et al., 1980a, 1980b; Koek and Slangen, 1982; Krimmer et al., 1984; Picker et al., 1990; Young et al., 1992; Picker et al., 1992; Zhang et al., 2000) and in the same rats after retraining at a lower dose (Craft et al., 1996). Figure 1 shows results from a classic study on fentanyl. In contrast, changes in ED_{50} values were not seen after training with the κ-opioid U50,488 (Picker et al., 1990), or the partial (mixed) agonists buprenorphine (Holtzman, 1997) and nalbuphine (Walker and Young, 1993). However, full and partial agonists do not seem to have been compared directly within a study.

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Studies in rodents have also yielded evidence for qualitative changes in patterns of generalisation at different training doses. Full generalisation to partial agonists was apparent in rats at low training doses of the full μ-agonists morphine and fentanyl, whereas at higher training doses there was often partial or no generalisation to partial opioid agonists (Shannon and Holtzman, 1979; Picker et al., 1990; Young et al., 1992; Picker et al., 1992; Zhang et al., 2000). Findings were similar with morphine discrimination established by taste aversion conditioning (Grabus et al., 1999). Comparisons of generalisation profiles to non-opioid compounds produced varying results, with some studies suggesting retention of specificity at low training doses (Koek and Slangen, 1982) whereas others indicated reduced specificity (Shannon and Holtzman, 1979; Colpaert et al., 1980b; Picker et al., 1990). Holtzman (1997) showed increased generalisation to the partial agonists pentazocine and nalbuphine in rats trained with a low dose of buprenorphine. At a high training dose of the κ-agonist U50,488, rats generalised to other κ-agonists but not to μ-agonists, whereas at a lower training dose both μ- and κ-agonists generalised, together with increased responding to non-opioid agents (Picker et al. 1990). In contrast, Broqua et al. (1998) did not find generalisation to morphine from a low training dose of U50,488. In pigeons, increased sensitivity at low training doses was seen consistently with the full and partial agonists (Koek and Woods, 1989; Gauvin and Young, 1989; Picker et al., 1993; Cook and Picker, 1998); in these studies, specificity was sometimes, but not always, retained.

There is also evidence for qualitative changes in opioid discrimination in pigeons as a function of training dose. Picker (1991) identified a naloxone-sensitive opioid component in discrimination of low doses of (−)-NANM (N-allylnormetazocine, SKF-10,047) whereas a large dose was predominantly PCP-like. Interestingly, by comparing data for different training doses of fentanyl, Picker et al. (1993) were able to identify three groups of opioids, i.e. (i) those substances that generalised fully at both doses, with steep dose-response curves and few inter-animal differences; (ii) those generalising fully with low training doses but to a slightly lesser extent with a large dose, with shallower slopes and marked inter-animal differences and (iii) those generalising with the low dose only, with shallow dose-response curves, large inter-animal differences and able to antagonise a high training dose of fentanyl. These different response patterns correlated with differences in intrinsic efficacy at μ-opioid receptors (Picker et al., 1993). Similarly, when subjects were trained on a low dose of morphine, increased generalisation to cyclazocine and (−)-NANM emerged (Cook and Picker, 1998). An absence of full generalisation from a high training dose of fentanyl to meperidine and profadol may have been a consequence of rate-decreasing effects of these substances mediated through non-opioid mechanisms (Picker et al., 1994). Quantification of antagonism has also been valuable in this area; for example, naltrexone antagonised both low and high doses of fentanyl with pA_2 values of 7.6 and 7.5 respectively, suggesting that similar receptors were involved (Zhang et al., 2000).

Studies of dose versus dose discrimination also shed light on the role of training dose. Partial μ- and κ-agonists typically generalised with a low training dose in rats trained with fentanyl or bremazocine but antagonised a higher training dose (Colpaert and Janssen, 1986; Smith and Picker, 1995). Results compatible with those of the preceding studies were obtained in elegant three-response procedures in pigeons and humans trained to discriminate between saline and each of two doses of a μ-agonist (Vanecek and Young, 1995; Jones et al., 1999).

To summarise, quantitative changes associated with training dose were apparent, with leftward shifts in dose-response curves seen in almost all studies of training with full μ-opioid agonists in rats and pigeons and with a partial agonist in pigeons. Results were inconsistent for partial agonist training in rats, and a shift was not seen in one study involving training with a κ-opioid in pigeons. Qualitative changes were also seen in both

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species, consisting primarily of increased generalisation to partial agonists when the training dose of a full agonist was low. However, specificity of stimulus control was not always preserved at low intensities of opioid receptor stimulation.

Alcohol

Ethanol is the most studied form of alcohol in drug discrimination procedures. The effect of ethanol training dose on quantitative and qualitative aspects of ethanol discriminative stimulus effects have been well documented both within and between subjects. Between subjects, the acquisition of ethanol discrimination consistently required fewer training session at higher doses in both rats (Overton, 1974; Grant and Colombo, 1993a; Colombo et al., 1995; Green et al., 1997; Green and Grant, 1998, 1999; Bowen et al., 1999a; Quertemont and Grant, 2002; Quertemont et al., 2003; Szeliga and Grant, 1998; York, 1978) and monkeys (Grant et al., 2000). The widest range of training doses studied under identical conditions was with a T-maze by Overton (1974) and encompassed 0.06–2.5 g/kg, requiring 500 and 20 trials, respectively (fig. 2). A very similar effect of dose range (0.33–0.99) on trials (100–20) was found with a two-lever operant procedure (York, 1978). Typically, there was an inverse relationship between ethanol training dose (range 0.8–2.0 g/kg) and the ED_{50} of ethanol substitution, although the differences were generally not statistically significant (Colombo et al., 1995; Grant et al., 1997; Green and Grant, 1998, 1999; Quertemont and Grant 2002; Quertemont et al., 2003; Ginsberg and Lamb, 2005). Further, in the studies cited above, the ethanol training dose generally did not have a significant effect on rates of responding, except with training doses over 2.25 g/kg (Overton, 1974).

Ethanol is a unique drug for examining the qualitative effects of training dose because the range of compounds that generalise to alcohol encompasses many pharmacological classes, and this lower specificity is not necessarily restricted to a lower training dose. A composite of most discrimination outcomes shows that $GABA_A$ positive modulators, NMDA antagonists and 5-HT agonists all substitute for ethanol (reviewed in Grant, 1999). However, direct $GABA_A$ agonists (Grant and Colombo, 1993a), neuroactive steroids with activity at NMDA receptors (Bowen et al., 1999a, 1999b), taurine (Quertemont et al., 2003), acetaldehyde (Quertemont et al., 2002), morphine (Grant and Colombo, 1993c, Szeliga and Grant, 1998), voltage-sensitive calcium antagonists (Green and Grant, 1999; Green-Jordan and Grant, 2000) and γ-hydroxybutyric acid (Helms et al., 2008b) fail to generalise across a range of training doses of ethanol. Thus, although ethanol is a mixed discriminative stimulus, it still retains pharmacological specificity, and this specificity is not linear with training dose.

The drugs that substitute for lower but not higher ethanol training doses are barbiturates (Grant and Colombo, 1993a; Grant et al., 1993; York, 1978), neuroactive steroids (Bowen et al., 1999), γ-hydroxybutyrate (Colombo et al., 1995) and 5-HT agonists (Grant and Colombo, 1993b; Grant et al., 1997; Green and Grant, 1998) in rats, and benzodiazepines (Grant et al., 2000; Helms et al., 2008b) in monkeys. However, this was not the case for the $GABA_A$ neuroactive steroid anaesthetic alphaxalone, which showed substitution at both lower and higher training doses in rats (Ginsberg and Lamb, 2005). In contrast to this substitution pattern, NMDA antagonists appeared to generalise more at higher than lower training doses in rats (Grant and Colombo, 1993, Grant et al., 1993) and monkeys (Vivian et al., 2002) but again, with some exceptions (Green and Grant, 1998).

Ethanol training dose also affects the ED_{50} of substitution differentially, with a lower ethanol training dose resulting in lower ED_{50} for pentobarbital (Grant and Colombo, 1993c; Green and Grant, 1998), the 5-HT agonists mCPP, TFMPP and Ru24969 (Grant and Colombo, 1993b; Grant et al., 1997) and the neuroactive steroids alphaxalone (Ginsberg and

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Lamb, 2005) and allopregnanolone (Bowen et al., 1999a). Similar to these findings in rats, monkeys also exhibited lower ED_{50} values for pentobarbital and allopregnanolone, using 1.0 g/kg as compared with 2.0 g/kg ethanol as a training dose (Grant et al., 2000, Helms et al., 2008a). In contrast to the $GABA_A$ positive modulators, higher ED_{50} doses were associated with 1.0 g/kg ethanol training as compared with 2.0 g/kg ethanol training in the substitution of the NMDA antagonists (+)3-(2-carboxy-piperazin-4-propyl)-1-propenyl-1-phosphonic acid (CPP) and dizocilpine; this was also the case for the dissociative anaesthetics ketamine and PCP in rats (Grant and Colombo, 1993a; Green et al., 1997), but not in monkeys (Vivian et al., 2002). In general, both qualitative and quantitative aspects of stimulus generalisation suggested a differential effect of ethanol training dose, with lower training dose cues mediated by positive $GABA_A$ and 5-$HT_{1B/2C}$ modulation and higher training dose cues more sensitive to the effects of dissociative anaesthetics.

Within-subject differences in the training dose of ethanol have been primarily assessed in rats trained to discriminate ethanol in a 3-lever ‘dose versus dose versus no drug’ procedure, where neuroactive steroids that are $GABA_A$ positive modulators show greater qualitative and quantitative substitution for 1.0 g/kg ethanol compared to 2.0 g/kg ethanol (Bowen et al., 1999b). Another approach to within-subject effect of training dose was to train rats initially to a low dose of ethanol versus water and than retrain to a higher dose, or vice-versa (Green and Grant, 1998). Raising the training dose increased the ED_{50} of pentobarbital and dizocilpine, while eliminating the substitution of TFMPP, whereas lowering the training dose lowered the ED_{50} of pentobarbital and dizocilpine and revealed substitution of TFMPP. This was taken as evidence for an effect of training dose on overshadowing among the component elements of the ethanol cue (Green and Grant, 1998). Overshadowing is said to occur if conditioning to a relatively weak stimulus is attenuated when it is always presented in combination with a more intense stimulus (Mackintosh, 1974); application of the concept in this area is based upon evidence for overshadowing of one drug by another in experiments where mixtures of dissimilar substances served as training stimuli (Mariathasan and Stolerman 1993; White and Stolerman 1996). An interesting twist on the within-subject approach was to test the substitution of ethanol during different phases of the menstrual cycle in monkeys, in order to address the potential contribution of circulating progesterone on sensitivity to ethanol (Grant et al., 1997). Specifically, in the luteal phases where progesterone is elevated the ED_{50} of ethanol substitution in lower compared to the follicular phase, where progesterone is very low (Grant et al., 1997), but this effect held only for 1.0 g/kg training dose of ethanol and not for a higher ethanol training dose or for the substitution pattern of midazolam (Green et al., 1997). In summary, within-subject studies of ethanol training dose reflect the general findings of drug versus vehicle discriminations and further allow the investigation of learning or additive physiological factors in both qualitative and quantitative discriminative stimulus effects.

GABA-mimetics

Barbiturates

The most widely studied barbiturate across training doses was pentobarbital, but limited evidence also exists for phenobarbital. Both rats (Overton, 1975, 1977) and gerbils (Järbe and Swedberg, 1998) consistently reached discrimination criteria in fewer sessions when trained on relatively high doses of pentobarbital. An exception was noted with the highest pentobarbital training dose in rats, a discrepancy probably attributable to the marked suppression of response rates (Ator and Griffiths, 1989). An assessment across phenobarbital training doses in rats revealed a similar inverse relationship between training dose and sessions to criteria (fig. 2). Greater discrimination accuracy was obtained with higher pentobarbital training doses, regardless of whether a ‘drug versus no drug’ procedure in parallel groups (De Vry and Slangen, 1986b; Järbe and Johansson, 1984) or a three-

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choice ‘dose versus dose versus no drug’ approach (McMillan et al., 2001) was utilised. Low pentobarbital training doses frequently engendered leftward shifts in dose-response curves (or lower ED_{50} values) when compared to higher ones (Ator and Griffiths, 1989; McMillan et al., 2001; De Vry and Slangen, 1986b).

McMillan et al. (2001) trained pigeons to discriminate pentobarbital in a three-lever ‘dose versus dose versus no drug’ procedure. Partial to full substitution by the benzodiazepine chlordiazepoxide was observed, but only for responding on the low dose-appropriate lever. In contrast, two-lever ‘drug versus no drug’ discrimination procedures in rats demonstrated that chlordiazepoxide and lorazepam fully substituted for both low and high pentobarbital training doses, with the generalisation curve for both benzodiazepines shifted to the left as the magnitude of the training dose decreased (Ator and Griffiths, 1989; De Vry and Slangen, 1986b). An additional ‘drug versus drug’ T-maze procedure in gerbils featured three training groups with low, medium or high pentobarbital doses discriminated from a fixed chlordiazepoxide dose (Järbe and Swedberg, 1998). Notably, the 5 and 15 mg/kg training doses of pentobarbital occasioned a high percentage of correct first-trial choices whereas the medium dose (10 mg/kg) was indistinguishable from the chlordiazepoxide training dose. The three-lever procedures suggest that the qualitative characteristics of pentobarbital change as a function of training dose.

Benzodiazepines

The prototypical benzodiazepines used in studies examining training dose as an independent variable are chlordiazepoxide, diazepam, midazolam, and lorazepam. Two stand-alone investigations provide preliminary insights into the role of training dose for the α_1-subunit selective agonist alpidem (Sanger and Zivkovic, 1994) and the partial inverse agonist β-CCE (Rowlett et al., 1999). Numerous studies demonstrated that benzodiazepine training dose magnitude was inversely proportional to the number of sessions to discrimination criteria in rats (Bruner and Anderson, 2009; De Vry and Slangen, 1986b; Shannon and Herling, 1983; Tang and Franklin, 1991; Sanger and Zivkovic, 1994; Rowlett et al., 1999) and gerbils (Järbe and Swedberg, 1998). It is similarly well documented that lower benzodiazepine training doses are associated with a leftward shift in the dose-response curve (i.e., lower ED_{50}) when compared to higher doses of the same training drug in rats (Ator and Griffiths, 1989; De Vry and Slangen, 1986b, 1986b; Bruner and Anderson, 2009; Sannerud and Ator, 1995a, 1995b; Shannon and Herling, 1983; Tang and Franklin, 1991; Sanger and Zivkovic, 1994; Rowlett et al., 1999) and humans (Rush et al., 1995). When reported, maximal discrimination accuracy was found to be greatest for the higher benzodiazepine training doses (Bruner and Anderson, 2009; De Vry and Slangen, 1986b; Shannon and Herling, 1983).

Generalisation of the barbiturate pentobarbital for chlordiazepoxide (De Vry and Slangen, 1986b) and diazepam (Shannon and Herling, 1983; Tang and Franklin, 1991) was found at both low and high training doses, whereas pentobarbital only partially substituted for a low training dose of lorazepam while producing no high dose-appropriate responding (Ator and Griffiths, 1989). This discrepancy may be explained by the relatively higher potency of lorazepam for the benzodiazepine binding site. A few studies suggested that low training doses of chlordiazepoxide (Bruner and Anderson, 2009), midazolam (Sannerud and Ator, 1995a), and the partial inverse agonist β-CCE (Rowlett et al., 1999) are less selective because negative pharmacological controls (i.e., psychostimulants) were found to partially substitute for the low but not the high training doses. Additional evidence for qualitative differences across training dose magnitude stems from antagonism tests. The antagonist flumazenil (Ro-1788) partially substituted for a low chlordiazepoxide training dose, but was also demonstrated to block a high chlordiazepoxide training dose to a greater extent than a low one (De Vry and Slangen, 1986a). A similar scenario was reported for the antagonist-

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like compound U-78875 and training doses of diazepam (Tang and Franklin, 1991). In summary, the cue produced by high training doses of agonists and partial inverse agonists exhibits greater specificity for benzodiazepine receptors.

γ-Hydroxybutyric acid

Gamma-hydroxybutyric acid is an endogenous ligand that acts through specific GHB receptors as well as $GABA_A$ and $GABA_B$ receptors following its metabolic conversion to GABA. Three studies established GHB discriminations in both rats and pigeons using food-reinforced T-maze and 2-lever discrimination procedures, respectively. Higher training doses of GHB were associated with more rapid acquisition of discrimination criteria and rightward shifts in dose-response curves (Koek et al., 2006; Colombo et al., 1995, 1998). It was also reported that the highest GHB training dose in pigeons achieved the greatest maximal discrimination accuracy (Koek et al., 2006). While $GABA_B$ receptor involvement persisted across training doses (as evidenced by both substitution with an agonist and blockade with an antagonist), partial substitution with diazepam-sensitive and -insensitive $GABA_A$ receptors agonists waned as the training dose increased (Colombo et al., 1998; Koek et al., 2006). These findings suggest that the pharmacological specificity of GHB discrimination narrows with higher training doses. The antagonist NCS-382 completely blocked GHB-appropriate responding at two training doses in rats (Colombo et al., 1995). while in pigeons NCS-382 failed to block either training dose and even partially substituted at low training doses (Koek et al., 2006).

Nicotine

Studies in rats, mice and humans have examined the impact of varying the training dose of nicotine. Discrimination of higher doses of nicotine in rats was acquired more rapidly and remained more accurate than discrimination of low doses, indicating a quantitative effect related to training dose (Hirschhorn and Rosecrans, 1974; Chance et al., 1977; Stolerman et al., 1984; Gasior et al., 1999). In most studies ED_{50} values also increased with training dose (Chance et al., 1977; Meltzer et al., 1980; Stolerman et al., 1984). Figure 3 illustrates this relationship using ED_{50} data for rats and mice from multiple publications. One study did not at first detect any differences between ED_{50} values, but a difference was found when the dose-response curves were re-determined in the same animals (Gasior et al., 1999). Possible qualitative differences in nicotine discrimination as a function of training dose have been explored to a limited extent. The nicotine antagonist mecamylamine was approximately equipotent in blocking discriminations maintained at two dose levels of nicotine in rats (Hirschhorn and Rosecrans, 1974). Chance et al. (1997) found partial generalisation to amphetamine at each of three nicotine training doses. Stolerman et al. (1984) observed more generalisation to the nicotinic agonists cytisine and anabasine at a low training dose of nicotine, an observation that was attributed to actions of the low dose on high-affinity nicotinic receptor subtypes; there was no generalisation at the low training dose to several non-nicotinic drugs, suggesting that specificity of the discrimination may not have been lost. Gasior et al. (1999) carried out tests with selective dopamine agonists and uptake inhibitors but did not find evidence for a qualitative change in nicotine discrimination.

The experiments discussed above used conventional, two-lever drug discrimination procedures. Murray and Bevins (2007) trained rats with different doses of nicotine as conditioned stimuli in a task requiring entries into a receptacle where sucrose solution was presented. The procedure appears functionally similar to one-lever operant conditioning techniques although it was interpreted in Pavlovian terms as a goal-tracking experiment. Rates of acquisition and ED_{50} values for nicotine were similar at all training doses, but potential differences may have been obscured by unconditioned drug-induced changes in

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responding; one-lever operant discrimination procedures were abandoned long ago due to the confounding of discriminative and response rate effects.

Mice of the C57BL/6 strain acquired nicotine discrimination more rapidly at higher training doses (Stolerman et al., 1999, 2004; Shoaib et al. 2002). Mecamylamine blocked nicotine discrimination at all three training doses (Stolerman et al. 1999).

Human subjects are able to discriminate nicotine delivered by means of a nasal spray. Perkins et al. (1996) compared two training doses of nicotine and obtained results that were strikingly similar to the findings discussed above for animals.

Glutamate Receptor Ligands

The dissociative anaesthetics PCP and ketamine are thought to act primary through antagonism of NMDA glutamate receptors. PCP is the most widely studied drug of this class across training doses. The relevant studies all employed a two-lever operant conditioning procedure in rats with training of ‘drug versus no drug’ discriminations unless otherwise noted. PCP discriminations met acquisition criteria more rapidly as a function of increasing training dose (Beardsley et al., 1987; Beardsley and Balster, 1988; Jackson and Sanger, 1988). A similar relationship was observed for both PCP and ketamine training doses within a T-maze shock-escape procedure (Overton, 1975). Leftward shifts in dose-response curves were demonstrated for low PCP training doses compared to high ones (Beardsley et al., 1987; Beardsley and Balster, 1988; Jackson and Sanger, 1988), and this shift in potency held regardless of whether comparisons were made between training dose groups or within the same training group of pigeons that were serially re-trained with progressively lower PCP training doses (fig. 4). A heightened discriminative accuracy (or decline in percentage response error) for PCP at high training doses versus lower ones was reported in two studies (Beardsley et al., 1987; Mansbach and Balster, 1991), while no difference was demonstrated in a third study with pigeons (Koek et al., 1987).

The NMDA receptor antagonists dizocilpine and AP-5, the sigma agonist NANM, and the PCP derivative metaphit all generalised regardless of PCP training dose magnitude, and leftward shifts in the generalisation curves were observed at lower training doses in rats (Jackson and Sanger, 1988) and pigeons (Koek et al., 1987). In contrast, the competitive NMDA receptor antagonist CPP partially generalised to low and medium PCP training doses (0.56 and 1.25 mg/kg), but not to the highest training dose studied (3.0 mg/kg; Mansbach and Balster, 1991). While no generalisation to pentobarbital was observed for any training dose of PCP in pigeons (Koek et al., 1987), this barbiturate did fully substitute for the lowest, but no other, training dose of PCP in rats (Mansbach and Balster, 1991). Collectively, these findings suggest that high training doses of PCP impart the greatest pharmacological specificity.

Although one study examined the role of training dose in the discrimination of the non-competitive NMDA antagonist dizocilpine, limited testing was conducted and no discernable quantitative or qualitative characteristics were detected between training doses (Smith et al., 1999).

Hallucinogens and other ligands for serotonin receptors

The impact of training dose on the discrimination of hallucinogens such as lysergic acid diethylamide (LSD) was first studied by Cameron and Appel (1973) in rats, and most subsequent studies have also used rats. One group used pigeons to investigate the 5-HT_{1A} agonist 8-hydroxy-(2-di-*n*-propylamino)-tetralin (8-OH-DPAT) that has been used extensively in studies of hallucinogenic and other drugs (Wolff and Leander, 1997, 1998).

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Mice were also trained at different doses of LSD (Winter et al., 2005) but there were no systematic comparisons across training doses.

Investigations in rats and humans have found that the dose-response curve for LSD shifts leftward at lower training doses, leading to reduced ED_{50} values (Greenberg et al., 1975; Nielsen et al., 1982; White and Appel, 1982a, 1982b). In some instances, the slope of dose-response curves was shallower at low training doses (e.g. White and Appel, 1982a; Nielsen et al., 1982). Leftward shifts of the dose-response curve for 8-OH-DPAT have also been found after training with 8-OH-DPAT in pigeons (Wolff and Leander, 1997) and in tests of generalisation from LSD to the 5-HT agonists quipazine, 8-OH-DPAT and 5-OMeDMT in rats (White and Appel, 1982a; Young et al., 1983; Ybema et al., 1993, 1994). After training with low doses of the 5-HT_{1A} partial agonist buspirone, leftward shifts of its dose-response curve were observed in rats (Ator, 1991) and humans (Rush et al., 1995).

Qualitative features of the LSD stimulus also vary with training dose. Notably, the extent of generalisation to quipazine and to 5-HT partial agonists increased at low training doses (White and Appel, 1982a). Nielsen et al. (1982) showed that the full 5-HT_2 antagonists pirenperone and ketanserin blocked both high- and low-dose LSD cues, whereas the partial agonist pizotifen completely blocked only the low-dose cue, findings compatible with observations of Colpaert et al. (1982) and Colpaert and Janssen (1983). However, White and Appel (1982a) found that the partial agonists methiothepin and cyproheptadine partially blocked all training doses of LSD. Further tests with 5-HT agonists and antagonists with predominantly peripherally-acting 5-HT ligands suggested that peripheral actions of LSD may have contributed more to the low-dose cue (White and Appel, 1982a). Pizotifen produced full block of 5-OMeDMT when the discrimination was established at a small dose, but even a much larger dose did not block discrimination with a larger training dose; these and other data of Young et al. (1983, 1986) may perhaps be understood by taking account of the partial agonist properties of some of the substances used. The specificity of the LSD cue seems to be retained at low training doses, as determined from generalisation tests with dopamine agonists and antagonists (White and Appel, 1982a).

In an elegant application of drug versus drug discrimination methodology that yielded orderly and readily interpretable data, White and Appel (1982b) trained LSD versus lisuride, a dopamine agonist. Different groups of rats were trained with a fixed dose of LSD against one of three doses of lisuride. Apomorphine generalised fully with lisuride in all groups. Quipazine generalised with LSD except when the training dose of lisuride was so large relative to that of LSD that the latter contributed little to the discrimination.

Cannabinoids

Studies have used between- and within-subjects designs in rodents to examine quantitative differences in Δ^9-tetrahydrocannabinol (THC) discrimination with training dose. Some reported smaller ED_{50} values at lower doses while others did not (Järbe et al., 1998, 2006a, 2006b, 2010). Anandamide does not substitute for THC at any training dose, yet anandamide analogues fully generalise and exhibit smaller ED_{50} values at lower training doses (Järbe et al., 1998, 2001). CB1 antagonists block THC discrimination and rimonabant may be more potent at lower training doses (Järbe et al., 2006a, 2010). Overall, CP-55940 establishes the most potent CB1 cue, followed by THC, AM-1346 and methanandamide (Järbe et al., 1998, 2006b; De Vry and Jentzsch, 2003). Morphine does not substitute at any training dose yet (+)-amphetamine partially generalises with low doses (Järbe et al., 2006b, 1998, 2009).

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Together the findings illustrate equivocal evidence for quantitative and qualitative differences in the stimulus effects of high and low THC training doses yet reveal variation in the interoceptive effects of CB1 agonists.

Antidepressants

Zhang and Barrett (1991) reported no difference in acquisition of imipramine discrimination between groups of pigeons trained at two doses, yet the low dose group exhibited smaller ED_{50} values. Overall, the high and low training doses did not differ qualitatively. Other tricyclic antidepressants generalised completely in both groups although the low dose group exhibited enhanced sensitivity. Cocaine, amphetamine, nomifensine, tomoxetine and bupropion, but not a selective dopamine reuptake inhibitor, substituted for imipramine, suggesting some importance of both noradrenergic and dopaminergic mechanisms in the imipramine stimulus. Fluoxetine did not generalise, yet 5-HT_{1A} receptor agonists did, indicating that imipramine probably produces some effects similar to these compounds. Finally, scopolamine, a muscarinic antagonist, generalised with the high training dose of imipramine. Jones et al. (1980) reported that acquisition of bupropion discrimination was dose-related; performance at the lower doses was unstable and differences in the bupropion stimulus as a function of training dose were not investigated further.

Antipsychotics

Dose-response curves for discriminative stimulus effects of the second-generation antipsychotic clozapine in rats were shifted leftwards at low training doses (Goudie et al., 2004; Prus et al., 2004). However, studies of the qualitative nature of the clozapine cue have yielded complex results. Low-dose clozapine discriminations generalised fully to the second-generation antipsychotics zotepine and melperone, but not to the first generation antipsychotic haloperidol (Goudie et al., 2004; Porter et al., 1999; Prus et al., 2004). The higher-dose discrimination generalised fully to melperone, but not to zotepine or haloperidol. A low training dose of olanzapine showed no or full generalisation to first generation antipsychotics, whereas a higher dose generalised fully to antipsychotics of both generations (Porter et al., 2000). Studies of three-choice discriminations using two doses of clozapine and vehicle yielded different patterns of results (Prus et al., 2005, 2006). The low training dose generalised fully to quetiapine and sertindole but not to other first and second generation antipsychotics, whereas the higher dose generalised fully to olanzapine but not to any other antipsychotic that was tested. Rather then reflecting antipsychotic actions, the discriminations may have been associated with actions on particular receptors; the anticholinergics scopolamine and trihexyphenidyl and the polyvalent antidepressant mianserin have also been found to generalise (inconsistently) with olanzapine and clozapine (Porter et al., 2000; Prus et al., 2004). Thus, the training dose influences both quantitative and qualitative aspects of cues induced by some antipsychotic drugs, but a general rule relating to the nature of the qualitative changes cannot be discerned.

Conclusions

Quantitative aspects

Relationships between training dose and rate of acquisition or magnitude of stimulus control have been found for diverse drugs. Typically acquisition improves with dose up to a level above which drug-induced impairments of performance may have a deleterious impact. Most often, sensitivity, as measured by ED_{50} values from dose-response determinations, increases when training dose is reduced. The mechanism of the change in sensitivity is commonly assumed to be a consequence of the training itself rather than of the different overall exposure to drug. Future research could attempt to distinguish such effects from

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those of training at varying doses, taking into account the larger numbers of training sessions that are sometimes needed with small training doses.

A small number of instances were identified where ED_{50} values did not decrease with training dose. These include studies with opioid partial agonists, nicotine or cannabinoids. In some cases training dose may not have been varied over a sufficiently wide range. In others, bias may have been introduced; poorly performing subjects are found with increasing frequency as training dose declines and if they are excluded, effects of small training doses on ED_{50} values and slopes of dose-response curves may be masked. Thus, subject selection may impact on the validity of conclusions about the relationship of sensitivity (ED_{50}) to training dose. It also seems inevitable that slopes will decline as the training dose approaches non-discriminable levels, at which point drug-lever responding will be at chance levels and dose-response curves will be flat. The ratio of the training dose to the ED_{50} in the same animals is rarely presented but it may be an additional useful metric related to slope. In most investigations subject selection is not an issue because the aim is to obtain subjects that perform well so that reliable data can be obtained during generalisation tests with putative agonists and antagonists.

The reduced ED_{50} at small training doses has implications for studies where different groups of subjects (e.g. different strains, sexes, genetically modified and wild-type animals) are compared for apparent sensitivity to the training drug. It is conceivable that real group differences may be masked: if one group is less sensitive to the training drug, the expected increase in ED_{50} might be wiped out by an opposing decrease caused by training with the equivalent of a smaller dose. This is relevant to a study where sophisticated receptor-mechanism explanations were put forward to explain negative results in a comparison of strains of rats that differed in several other procedures (Morgan et al. 1999). In such cases, it seems necessary to use more than one training dose so that the speed of acquisition, which consistently increases with training dose, can be taken as the metric.

Qualitative aspects

Numerous instances of variation in generalisation profiles as a function of training dose have been reported for several species. However, there are many gaps in the evidence; for example, there are studies with rats and pigeons in which the training dose of an opioid is systematically varied but none with monkeys. Nevertheless, several general patterns have emerged from these reports. Firstly, subjects trained on full agonists often show greater generalisation to partial agonists when the training dose is low and these effects are often accompanied by orderly findings for antagonism; drugs that substitute best for low training doses tend to attenuate the stimulus effects of high training doses. This pattern is seen with opioids and benzodiazepines and to some extent with LSD (i.e. in tests with full and partial 5-HT agonists). Secondly, there is a common tendency for specificity to be reduced at low training doses e.g. with opioid partial agonists and PCP, although it is not universal. Subjects maintained on small training doses of PCP generalised to CPP, as expected from their shared NMDA antagonist actions, but there was also generalisation to a barbiturate, suggesting some loss of specificity. Evidence for reduced specificity at low training doses has not yet been obtained for cannabinoids and LSD, whereas the relative dearth of studies with antidepressants and antipsychotics precludes firm conclusions about them.

Another pattern that has been observed in some studies with low training doses of certain drugs is a decrease in generalisation to agents of one class but an increase to those of another. Such findings imply shifts between the relative salience of stimulus elements originating at different classes of receptor. For example, when the training dose is low, ethanol generalises to agents from several pharmacological classes (barbiturates, benzodiazepines, neuroactive steroids and some 5-HT agonists), but tests with other agents

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suggest that this is not due to a global loss of specificity. In contrast, large training doses of ethanol show increased generalisation to NMDA antagonists. A rather different pattern emerges with amphetamine: generalisation to apomorphine appears to increase with training dose whereas that to para-hydroxyamphetamine decreases, the latter suggesting a shift from peripheral to central origins for the amphetamine cue, as may also be the case for the LSD cue. Curiously, data for generalisation to para-hydroxyamphetamine at different training doses of cocaine do not seem to be available.

Summary

This review has identified many studies in which the training dose influenced attributes of drug-produced discriminative stimuli. The quantitative changes are easier to explain and comprise increases in the rate of acquisition and robustness of stimulus control at large training doses, accompanied by reduced sensitivity. as shown by larger ED_{50} values. Further insights may be obtained by more extensive investigations of drug-induced stimuli built around the principles of signal detection theory, as applied to exteroceptive stimuli of different intensities, although altering the dose of a drug may influence not only the intensity of the stimulus that it produces but may also affect its qualitative nature. This review has shown that qualitative changes as a function of training dose are complex and appear to fall into three categories: (i) changes in profiles of generalisation between partial and full agonists; (ii) reduced specificity of some discriminations at small training doses and (iii) changes in the relative salience of actions mediated through different neurotransmitter systems or from central and peripheral sites. It is also notable that three-lever discrimination procedures incorporating ‘drug versus drug’ or ‘dose versus dose’ contingencies enabled detection of more subtle differences than the simple ‘drug versus no drug’ approach when they applied to the opioid, hallucinogen and barbiturate classes of drugs.

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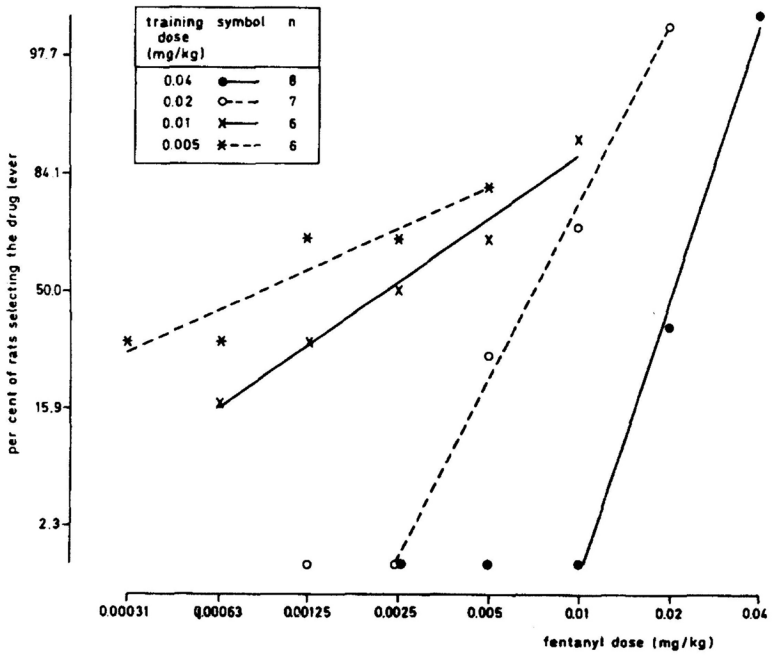

Fig 1.

Log-probit plot of dose-response curves in different groups of rats trained to discriminate fentanyl from saline at doses of 0.005, 0.01, 0.02 or 0.04 mg/kg in a two-lever, operant conditioning procedure with an FR 10 schedule of food reinforcement. The typical leftward shifts of the dose-response curve at lower training doses can be seen, as well as flattening of dose-response curves as the training dose approached levels that were too low to be discriminable (reproduced from Colpaert et al. 1980b, with permission from Elsevier).

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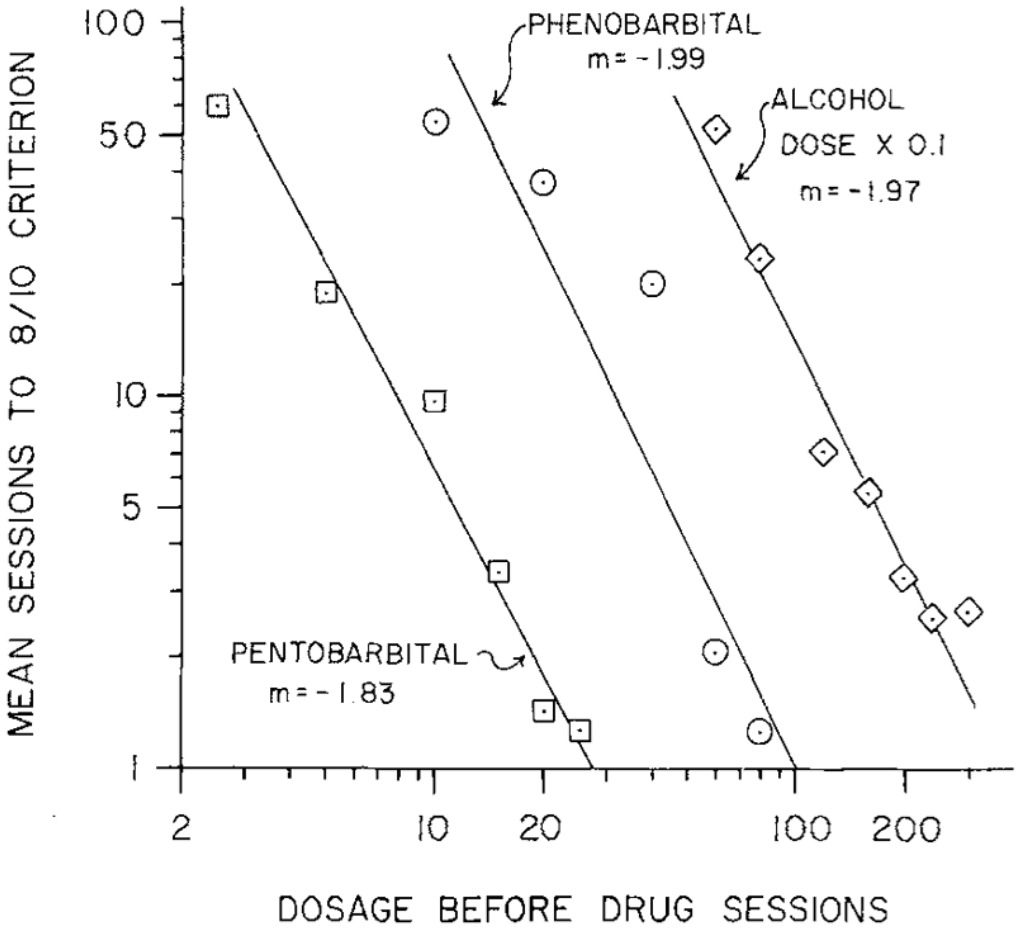

Fig 2.

Relationship between training doses and sessions to a criterion of discrimination performance for pentobarbital, phenobarbital and ethanol administered i.p. at the doses shown for rats in a T-maze shock-escape task. Criterion performance was eight correct first-trial choices during ten consecutive training sessions (fig. 1 from Overton, 1977, reproduced with kind permission of Springer Science+Business Media).

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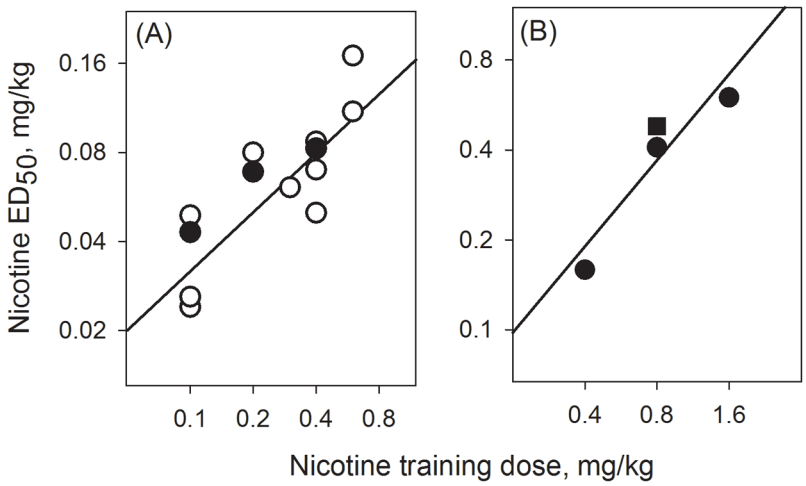

Fig 3.

Rat and mouse ED_{50} values from diverse studies showing the relationship with the training dose of nicotine. (A) results from ten studies in Sprague-Dawley rats showing that training with lower doses of nicotine was associated with lower ED_{50} values (○, data from Batman et al. 2005; Bondarev et al. 2003; Desai et al. 2003; Gasior et al. 1999; Le Foll & Goldberg 2005; Mansbach et al. 2000; Young & Glennon 2002 ; Young et al. 2006) and a within-study comparison of training doses in Lister hooded rats (●, Stolerman et al. (1984). (B) results from Stolerman et al. (1999) showing relationship of ED_{50} values with training dose in C57BL/6 mice (●), and results at a single training dose for DBA/2 mice (■). This figure has been modified from a similar one in Smith and Stolerman (2009) with kind permission of Springer Science+Business Media.

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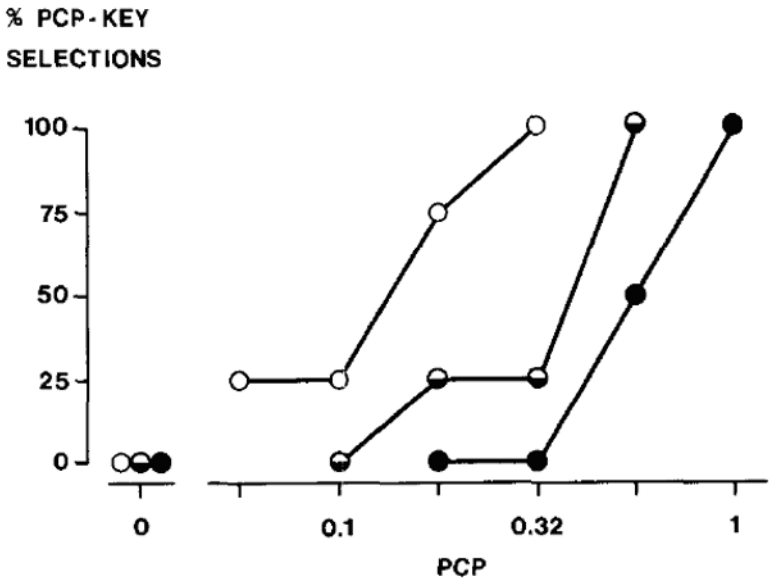

Fig 4.

Leftward shifts of dose--response curves as a function of training dose in pigeons trained to discriminate between phencyclidine and saline. The training dose was lowered progressively and a dose-effect curve was established at each training dose level in pigeons that met discrimination criteria at all training doses. Vertical axis: percentage of drug-key selections; horizontal axis: dose (mg/kg, i.m.). Training dose: ● 1.0 mg/kg; ◒ 0.56 mg/kg; ○ 0.32 mg/kg (reproduction of fig. 1 from Koek et al., 1987, with kind permission of Springer Science +Business Media).