Table 2. Half-lives ($t_{\frac{1}{2}}$), areas under the plasma concentration-time curves (AUC) and apparent plasma clearances (Clp) of *N*-desalkylprazepam after single oral doses of prazepam (30 mg ≡ 25 mg *N*-desalkylprazepam) to human subjects.

Subject No.*	$t_{\frac{1}{2}}$ (h)	AUC (μg h ml^{-1})	Clp† (litres h^{-1})
1 (41)	109	26·22	0·95
2 (27)	91	29·99	0·83
3 (20)	63	24·93	1·00
4 (23)	63	18·69	1·34
5 (39)	208‡	50·61	0·49
Mean (s.d.)	107 (60)	30·09 (12·17)	0·92 (0·31)

* The ages (years) of the subjects are shown in parentheses.
† Uncorrected (See text).
‡ On another occasion when this volunteer was dosed with prazepam, the measured half-life of *N*-desalkylprazepam was shorter, 96 h, and the clearance higher, 0·57 litres h^{-1}.

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Naloxone fails to block amphetamine-induced anorexia and conditioned taste aversion

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Some behavioural effects of amphetamine can be antagonized by naloxone (Holtzman & Jewett 1973; Holtzman 1974; Holtzman 1976; Dettmar et al 1978; Haber et al 1978). Such findings suggest that endorphin/catecholamine interactions may be important in the control of behaviour (Dettmar et al 1978; Haber et al 1978). However, naloxone/amphetamine interactions are *not* simple phenomena, having been reported to be species specific (Holtzman 1974, 1979a), although other data cast doubt on this notion (Dettmar et al 1978). They have also been reported to be behaviourally specific (Haber et al 1978) although this conclusion is also questionable (cf. Segal et al 1977; Dettmar et al 1978); and to occur only with low ($\leqslant$3 mg kg^{-1}) doses of naloxone (Dettmar et al 1978). Other authors have reported antagonism with much higher doses (Holtzman & Jewett 1973). Clearly, the data available on amphetamine/naloxone interactions are inconsistent. Nevertheless, much evidence supports the idea that catecholamine/endorphin interactions are important in mediating behaviour (e.g. Harris et al 1977; Iwamoto & Way 1977; Broekkamp et al 1979; Belluzi & Stein 1977; Katz & Carroll 1979; Amir et al 1979; Kelley et al 1980). The work reported here has further investigated naloxone/amphetamine interactions to clarify the significance of contradictory earlier reports. The first study described examined naloxone effects on amphetamine anorexia.

Female albino rats (200–250 g) housed in a light and temperature controlled room were habituated to an 18-h food deprivation schedule for 28 days, during which they received six i.p. injections of 0·9% NaCl (saline) to adapt them to handling and injection stress. They were then allocated to ten groups (n = 8) making up a complete 2 × 5 factorial design, all subjects receiving two injections on the day of anorexia testing. The first injection was saline or (+)-amphetamine 2·0 mg kg^{-1}. The second was either one of four doses of naloxone hydrochloride: 0·3 (n_1), 1·0 (n_2), 3·0 (n_3) and 10 mg kg^{-1} (n_4) or a saline control. Injection pairs were administered i.p. (2 ml kg^{-1}) within one minute, 30 min before food access. Amounts of food (lab chow) eaten were recorded 1, 2, 4 and 6 h after access. Some of the behavioural effects of the 2·0 mg kg^{-1} dose of (+)-amphetamine used have previously been reported to be antagonized by naloxone (Holtzman 1976; Segal et al 1977; Dettmar et al 1978).

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Amounts of food eaten by all groups are shown in Fig. 1.

These data were analysed by separate 2 × 5 ANOVAs at each sampling time. Amphetamine had a significant anorectic effect (smallest F = 10·9 at 6 h; df = 1,70; $P < 0.005$). At no sampling time was the naloxone dose level significant, nor was there a significant interaction between naloxone levels and amphetamine/saline treatment. Amphetamine clearly had a potent anorectic effect which was not antagonized by naloxone. We failed to detect any effect of naloxone itself on food intake, in contrast to other reports (Margules et al 1978; Holtzman 1974, 1979b; Frenk & Rogers 1979; Brands et al 1979). Holtzman (1974) reported that naloxone had a potent anorectic effect in rats, although in a later study (Holtzman 1979b) the drug had a strikingly weaker effect, a discrepancy that was attributed to the longer period of adaptation to restricted food access used in the second study. The effects of naloxone can be attenuated by stressors present at the time of injection (Stewart & Eikelboom 1979). Extended periods of adaptation to food deprivation, as used in the study reported above, may have modulated the pharmacological actions of naloxone by subjecting subjects to chronic stress, and might therefore account for the discrepancy between our data and those of other authors.

One possible explanation for the lack of an antagonistic effect of naloxone reported above relates to the finding that amphetamine-induced anorexia is thought to be mediated largely by central noradrenergic systems with dopaminergic systems playing only a minor role (Hoebel 1977). The naloxone/amphetamine interactions reported by other authors may have involved predominantly dopaminergic systems which were not involved in the anorexia study reported above. We therefore initiated a second study involving a different

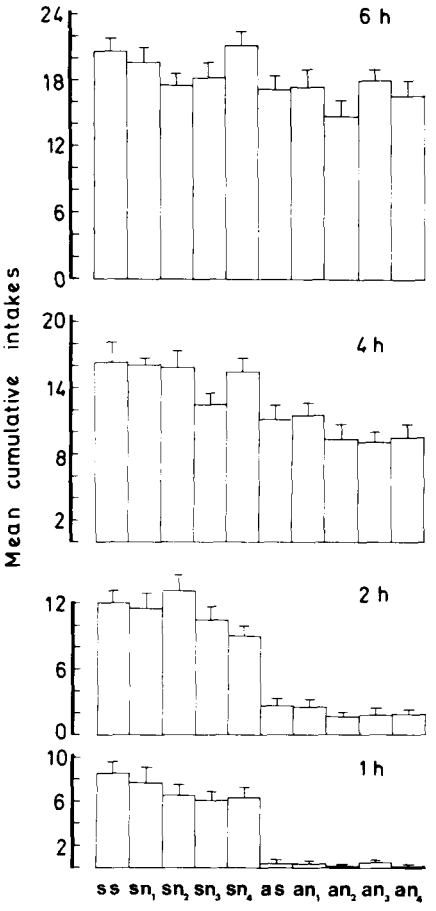

FIG. 1. Mean (and s.e.) cumulative amounts (g) of food consumed by subjects in each experimental group at each of four sampling times after initial food access. Group codes: 1st letter refers to injection of saline (s) or amphetamine (a); 2nd letter refers to injection of saline (s) or naloxone (n) at 1 of 4 doses. See text for details of drug doses.

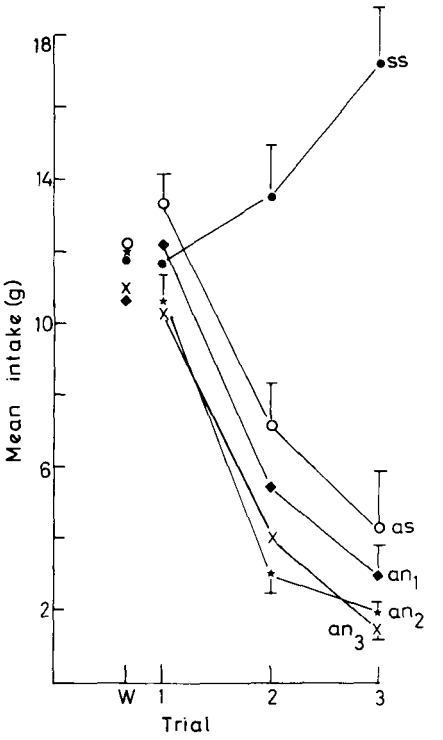

FIG. 2. Mean (and s.e.) amounts (g) of 0·1% saccharin solution consumed over Trials 1–3 for each experimental group. (Some standard errors have been omitted for clarity). Also shown (at W) are the mean baseline levels of water consumed on the day prior to Trial 1. Group codes: 1st letter refers to saline (s) or amphetamine (a) injection, 2nd letter refers to injection of saline (s) or naloxone (n) at one of three doses. See text for details of doses. The increase in fluid intake over Trials noted in the control (ss) group is attributable to reduction of a 'neophobic' response to saccharin (cf. Goudie et al 1978).

behavioural task: conditioned taste aversion (C.T.A.). In the C.T.A. paradigm a very wide variety of drugs, including amphetamine, will act as aversive stimuli (Goudie 1979). Amphetamine-induced C.T.A. is mediated in part by central dopaminergic systems (Grupp 1977; Lorden et al 1980). A study of the effects of naloxone on amphetamine-induced C.T.A. was consequently conducted.

Female albino rats (200–300 g) housed as described above were allocated to five groups (n = 7). For 7 days all subjects were habituated to a regime of 30 min water per day. On Day 7, baseline levels of water intake were recorded. Day 8 constituted Conditioning Trial 1; subjects received 30 min access to 0·1% saccharin solution, amounts consumed being recorded. A pair of drug injections (i.p.) was administered within 5 min of the end of the period of saccharin access. The first injection was (+)-amphetamine sulphate (2·0 mg kg^{-1}) or saline, the second injection was saline or naloxone hydrochloride at one of three doses: 1·0 (n_1), 3·0 (n_2) and 9·0 mg kg^{-1} (n_3). The complete study consisted of a control group which received two saline injections after saccharin intake (ss group), a group which received amphetamine followed by saline (as group) and three groups which received amphetamine followed by one of the three naloxone doses (an_1, an_2 and an_3 groups). One week after Trial 1, subjects received a second 30 min period of access to saccharin (Trial 2), after which intakes were recorded and the relevant treatments administered. A further week later subjects received a final period of saccharin access (Trial 3), intakes again being recorded. Between Trials subjects received 30 min of water daily. The basic C.T.A. procedure outlined above has been described in detail previously (Goudie et al 1978). Fig. 2 shows the fluid intakes of subjects in each group.

Baseline water intakes did not differ between groups ($F = 0{\cdot}45$, df = 4,30). Saccharin intake over Trials was analysed by a 3 × 5 repeated measures ANOVA. There were highly significant overall groups ($F = 27{\cdot}2$; df = 4,30; $P < 0{\cdot}001$) and Trials ($F = 70{\cdot}1$; df = 2,60; $P < 0{\cdot}001$) effects; as well as a highly significant interaction ($F = 14{\cdot}2$; df = 8,60, $P < 0{\cdot}001$). There were no group differences [Turkey HSD (a) multiple comparison tests, $\alpha = 0{\cdot}05$] on Trial 1, but on Trials 2 and 3 group as differed significantly from group ss but not from any of an_1, an_2 and an_3. Amphetamine clearly induced a significant C.T.A. in this study, but its effects were totally unaffected by naloxone treatment. These data provide no evidence for antagonism of amphetamine-induced C.T.A. by naloxone. Although naloxone has itself been reported to induce a weak C.T.A. in rodents (Stolerman et al 1978) this does not prevent it from atagonizing morphine-induced C.T.A. (LeBlanc & Cappell 1975; Van der Kooy & Phillips 1977). The failure of naloxone to block amphetamine-induced C.T.A. cannot therefore be attributed simply to intrinsic aversive actions of the drug itself.

In the two studies reported here naloxone failed to antagonize either of the behavioural effects of (+)-amphetamine that were studied. It is, of course, possible that antagonism might have been obtained had other dose combinations of (+)-amphetamine and naloxone been used. However, it should be stressed that doses of both drugs were chosen so as to be similar to those with which antagonistic effects have been reported from other laboratories. The data reported here might appear to provide little support for the idea that endorphin/catecholamine interactions are of importance in the control of behaviour. However, the major conclusion to be derived from this and related studies would seem to be that the antagonism by naloxone of (+)-amphetamine's behavioural effects is not a highly reliable phenomenon. In the context of these negative findings it is relevant to note that Huey et al (1980) have reported that in man naloxone fails to antagonize the behavioural effects of the psychostimulant methylphenidate. It has been noted previously that caution should be exercised in interpreting studies of naloxone/amphetamine interactions (Holtzman & Jewett 1973; Holtzman, 1974, 1976, 1979a). When antagonistic effects have been reported, examination of dose-response data indicates that such antagonism may differ *qualitatively* from that of narcotic agonists (Holtzman & Jewett 1973; Holtzman 1976). These considerations, coupled with the reported difficulties in antagonizing amphetamine's behavioural effects with naloxone, suggest strongly that the investigation of such interactions may be an unreliable method for analysing the role of catecholamine/endorphin interactions in the control of behaviour.

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Effects of neonatal capsaicin administration on the nociceptive response of the rat to mechanical and chemical stimuli

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Acute capsaicin treatment in adult rats has been shown to increase firing rates in peripheral sensory nerves involved in the transmission of nociceptive input due to chemical irritants or thermal stimuli, whereas the firing rate of those fibres involved in the transmission of impulses caused by light touch or mechanical stimuli is unaltered (Coleridge et al 1964). Treatment of rats with capsaicin on day 2 of life induces a selective degeneration of primary sensory neurons involved in the mediation of chemically-induced pain (Jancso et al 1977) and it has been reported that reaction times to thermal stimuli in hot-plate and tail-flick tests measured in these animals 3 months later are prolonged (Holzer et al 1979). Responses to mechanical stimuli remain unchanged (Jancso 1968).

The aim of the present study was to determine the effects of capsaicin treatment in neonatal rats on the nociceptive responses due to chemical and mechanical stimuli using two different test systems. The injection of irritant chemical substances into a lateral tail vein in the rat produces behavioural responses, the severity of which can be graded in a semi-quantitative manner using an arbitary 0–3 scale, where 0 represents no pain as indicated by the lack of any struggling or vocalization; 1 represents slight pain indicated by struggling; 2 represents moderate pain indicated by struggling and the rat turns in an attempt to bite the injecting needle; 3 represents severe pain as indicated by intense struggling and pulling away from the injection. In this latter phase, the rat also vocalizes. In this test, potassium chloride (10^{-1} M), hydrochloric acid (10^{-1} M) and bradykinin (10^{-5} M) produce marked behavioural effects. Hydrochloric acid was selected due to the reproducibility of responses with this agent. Pain were also determined in normal and yeast-inflamed rat paws using a Ugo Basile 'analgesy-meter', which is described by Swingle et al (1971).

On the second day of life, female rats (Alderley Park strain) were dosed with capsaicin (Sigma) 50 mg kg^{-1} or vehicle (0·5% cremophor EL; 2·0% DMSO in 0·9% saline) subcutaneously. Three months later, 0·05 ml of 10^{-1} M hydrochloric acid was injected into the lateral tain vein over a period of 20·0 s and an assessment was made of the behavioural response during the injection. Using the 'analgesy-meter', the pressure on the paw was increased at a rate of 16 g s^{-1} and respectively 16 × 2, 16 × 3, etc. according to the number of additional weights added, responses generally being obtained within 5–10 s, i.e. withdrawal of the paw by the rat. All experiments were performed using the same animals for each test with a one-week interval between the tests when pain thresholds were determined in rats with normal and inflamed paws. The operator was unaware of the treatment administered to each rat.

In the tail-vein injection test, capsaicin treatment resulted in an 81% decrease in the mean pain response (capsaicin-treated 0·4 ± 0·1 n = 7, vehicle-treated 2·0 ± 0·3 n = 7 $P < 0.01$ Student's unpaired t-test). In the rat paw-pressure test, capsaicin treatment resulted in a 63 and 72% increase in nociceptive threshold in rats with normal and inflamed paws respectively (Table 1).

These observations show that it is possible to detect differences in nociceptive thresholds between untreated and treated rats when subjected to both mechanical and chemical stimuli. This former result is at variance

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