LETTERS

What makes lorazepam different from other benzodiazepines?

In a recent issue of *The Journal of Physiology*, Di Lazzaro *et al.* (2005) reported that two benzodiazepines (BZs), lorazepam (2.5 mg p.o.) and diazepam (20 mg p.o.), had dissociated short latency afferent inhibition (SAI) effects, the former having reduced, while the latter, increased SAI. We would like to draw attention to the fact that this adds one more piece of important evidence to the already well-established atypical nature of lorazepam effects (see Pompéia *et al.* 2003*a*) for a reason that the authors may not have fully appreciated in their paper.

We have previously compiled reports that point to the atypical effects of lorazepam in contrast to that of other BZs (Pompéia *et al.* 2003*a*), which include both behavioural and physiological evidence. In terms of behavioural measures, lorazepam has an atypical profile in animal discrimination studies (see Ator & Griffiths, 1997; Ator & Kautz, 2000), as well as in investigations into human cognition. Contrary to what Di Lazzaro *et al.* seem to claim, diazepam does not have only 'minimal effects on memory'. Diazepam, as all BZs, leads to considerable deficits in a subtype of memory named episodic memory (Curran, 2000). In contrast to lorazepam, however, no other BZ, including diazepam, has been found to *consistently* impair another type of memory, repetition priming (for an exception see Vidailhet *et al*. 1994). Lorazepam also impairs visual perception in an atypical manner (see Pompéia *et al.* 2003*a*; and more recent publications Giersch & Herzog, 2004; Lorenceau *et al*. 2005), although diazepam has also been found to lead to larger visual effects than lorazepam (Boucart *et al.* 2000). Ingestion of acute doses of lorazepam have also been shown to result in: (a) less EEG fast activity as measured by dynamic brain mapping in relation to diazepam although lorazepam led to more pronounced side-effects (Itil *et al.* 1989); (b) atypical disruption of visual event-related potentials (ERPs) in comparison to flunitrazepam, a drug with comparable BZ receptor affinity, even when the doses of both drugs were equated following strict criteria (Pompéia *et al.* 2003*b*); and (c) reduced SAI contrary to diazepam, which increased it (Di Lazzaro *et al.* 2005).

It must be born in mind that most of the above-mentioned studies did not follow specific methodologies for selecting equipotent doses of lorazepam and the BZ with which it was being compared. Qualitatively different effects may be obtained by varying the dose of the same drug and may reflect test difficulty or sensitivity rather than qualitative differences between drug effects (Duka *et al.* 1996). A partial solution to this problem is to obtain a double-dissociation (i.e. each drug having larger effects in different tests; see Pompéia *et al.* 2003*b*) or to show opposite effects between drugs such as importantly attained in the paper of Di Lazzaro *et al*. Such demonstrations in purely physiological parameters make the case of lorazepam's atypical effects so much the greater because this type of data is not altered by effort, motivation, schooling or intelligence, as behavioural scores have been shown to be. Nevertheless, for confirmation of lorazepam's atypical SAI effects it would be adequate to have Di Lazzaro *et al.*'s findings replicated in a randomized, placebo-controlled, preferably within-subject study comparing the effects of lorazepam with those of another BZ. The use of different doses would also be of interest to rule out that lower doses and/or less potent drugs, as is the case of diazepam in relation to lorazepam, lead to a decrease in SAI while higher doses/more potent drugs increase SAI.

The reasons for the difference in effects of lorazepam *versus* other BZs, drugs which are chemically so similar, are unknown. Lorazepam's atypical profile has been tentatively ascribed to its pharmacodynamics although very little is still known of binding characteristics of BZ compounds to distinct receptor subtypes in different brain regions. We find that the most convincing justification for lorazepam's atypical effects is that it may display specific binding profiles to as yet uncharacterized BZ receptors since this has been proved true for drugs that have qualitatively different effects from others in their class (e.g. Lelas *et al.* 2000). The only partial evidence for this, however, was perspicaciously pointed out by Ator & Griffiths (1997) in respect to a publication by Sanger & Benavides (1993), who showed, but did not discuss, that lorazepam had markedly different potency throughout rat brain regions while other BZs did not. As lorazepam is one of the few BZs of non-synthetic origin that is found in brain, serum and milk of various species including man (Sand *et al.* 2000), one might even daringly presume that there may well be specific receptors for this drug.

In summary, physiological evidence mounts of the atypical profile of lorazepam effects. More work similar to that of Di Lazzaro *et al.*'s is needed so that it may be determined what makes this drug unique among other BZs, a finding that will certainly prove important to the better understanding of $GABA_A$ receptor physiology.

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