concentrates in fish fatty tissues) was correlated significantly to memory impairment. The full article appears in the June issue of *Environmental Health Perspectives,* a publication of the National Institutes of Health. [Schantz, S.L. et al. (2001) Environ. Health Perspect. 109, 605–611] DC

**Dodgy malaria drugs**

An investigation into the quality of antimalarials in South East Asia has identified serious problems, with drugs that are fake or past their shelf life as a consequence of inadequate storage conditions. Substandard treatments could increase a patients risk of death, increase side-effects or permit more rapid development of resistant varieties. A recent report in the Lancet tested over 100 samples of the artemisinin derivative artemunate, and found 29% contained no artemunate. Luckily, bogus packages are distinguishable from the real packages, and education might be key to eliminating the problem. [Newton, P. et al. (2001) Lancet 357, 1948–1950] KP

**New in neurology**

Around 5000 delegates gathered in London, UK on 17–22 June 2001 for the twelfth World Congress of Neurology. The congress covered a diverse range of issues, from the shortage of neurologists in the UK to revealing a genetic component to migraine and clues to the hangover headache. New results were revealed in the fight against bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jakob disease (CJD), and electrical impulse therapy was discussed as a new way to control epilepsy. The event was sponsored by The World Federation of Neurology, The Association of British Neurologists and The European Federation of Neurological Societies. KP

**Letters**

**Anxiolytic-like action of diazepam: which GABA_A receptor subtype is involved?**

The recent article by Rudolph and colleagues1 provided a comprehensive review of GABA_A receptor knock-out mouse lines and also discussed the use of mice with subtle single point mutations in their GABA_A receptor subunits (‘knock-in mice’). These animals have been used to further define which properties of benzodiazepines (BZs) are mediated by specific α-containing GABA_A receptor subtypes. However, caution is required in interpreting some of the behavioural data obtained from mice whose α-1, α-2- or α-3-subunits are insensitive to diazepam (i.e. α1H101R, α2H101R or α3H126R) because the anxiolytic models used (i.e. the elevated plus maze (EPM) and the light–dark box (LDB)) are locomotor dependent.

One consistent conclusion from studies with selective drugs and knock-in mice is that the α1-subtype mediates the sedative properties of BZ receptor agonists2,3. Recently, and somewhat unexpectedly, we found that diazepam increased activity in α1H101R knock-in mice when they were placed in a novel environment5. Crestani et al.4 confirmed this observation when mice were examined in a novel environment; the effect was absent in mice placed in a familiar environment2,4. Moreover, the α2-, α3- and α5-selective BZ receptor agonist L838417 stimulated activity equally in both wild-type and α1H101R knock-in mice3 when the environment was novel. Consequently, it is clear that in a novel environment diazepam induces a direct increase in locomotor activity mediated by the α2-, α3- or α5-subtype, an effect that is normally opposed by the sedative actions of diazepam at the α1-subtype. Thus, care is needed when interpreting data generated in locomotor-dependent tasks.

The usual measures of anxiolysis in the EPM are an increase in time spent on, and the number of entries to, the open arms. These measures can yield both false positive and false negative results depending on how drugs effect locomotor activity6. Similar arguments also apply to the LDB, where the main measure is the time spent in the lit area. Novelty is another important factor because the stimulant effects of diazepam might only be observed when the animals are in a novel environment and are unlikely to be observed if the animals are in a familiar environment6,7. These considerations suggest that there are alternative interpretations of the published data on α1-, α2- and α3-BZ-insensitive knock-in mice treated with diazepam2,4. As outlined above, there is general agreement in the literature that the α1-subtype is the primary mediator of the sedative and locomotor suppressant effects of BZ receptor agonists, but it is not known whether the α2-subtype or the α3-subtype stimulates locomotor activity in a novel environment. If the α2-subtype mediates the stimulatory effects then diazepam-treated α2H101R mice would be expected to be less active than wild-type mice, because there is no α2-mediated stimulation to offset α1-mediated decreases in activity. Similarly, if the α3-subtype mediates the stimulatory effects then α3H126R mice would be less active than wild-type controls. Thus, the lack of an ‘anxiolytic’ effect (i.e. increased open arm time or entries) in α2H101R mice reported by Löw et al.8 might be more related to hypoactivity than anxiolysis per se. Moreover, it is not possible to determine whether the increased open arm time and entries displayed by diazepam-treated α3H126R mice represent a real anxiolytic response or just an increase in locomotor activity6. Thus, analysis of the locomotor activity of these animals while on the EPM or in the LDB would help to clarify this point. Finally, the development of subtype-selective ligands with efficacy at only one of the α-subtypes would allow pharmacological confirmation of these findings in conventional laboratory animals and eventually in the clinic.

David S. Reynolds
Ruth M. McKeman
Gerard R. Dawson*
Merck Sharp & Dohme Research Laboratories,
The Neuroscience Research Centre, Terlings Park, Harlow, Essex, UK CM20 2QR.
*e-mail: gerry-dawson@merck.com

---

This month’s In Brief articles were written by David Cutler (mqbssdc2@fs1.scg.man.ac.uk) and Katharine Pestell (Katharine.Pestell@current-trends.com).
Anxiolytic-like action of diazepam: mediated by GABA_A receptors containing the α2-subunit

Response from Crestani et al.

Using a point-mutation strategy the anxiolytic-like effect of diazepam was recently attributed to GABA_A receptors that contain the α2-subunit. This finding was based on the lack of an anxiolytic-like response to diazepam in α2(H101R) mice but not of α3(H126R) mice in the elevated plus maze (EPM) and the light-dark box (LDB) tests. Because these tests involve locomotion, a direct drug-induced motor effect has to be excluded.

In their study on α1(H101R) mice, McKernan and colleagues showed that diazepam increased locomotor activity in α1(H101R) mice. In addition, in wild-type mice, diazepam was without effect on locomotor activity. The test conditions of enhancement of locomotion in α1(H101R) mice appears to be stress related. Under our experimental conditions of the LDB and EPM tests, diazepam did not display a stimulatory effect on locomotion. The argument put forward by Reynolds and colleagues therefore does not warrant an interpretation of the data different from that published previously.

References