Table 2. Mean ± s.e.m. period of latency for convulsions (s) induced by lignocaine according to the hour of administration in lignocaine alone and in lignocaine + flumazenil-treated animals. Statistical comparison by analysis of variance and cosinor analysis.

	Clock time (h)					
Groups	08	10	13	18	23	04
Lignocaine alone	148 ± 9	177 ± 14	150 ± 9	145 ± 7	128 ± 11	154 ± 11
Lignocaine + flumazenil	112 ± 7	123 ± 11	123 ± 8	114 ± 7	115 ± 10	129 ± 13
Analysis of variance	H:		$F = 1{\cdot}90$, $P = 0{\cdot}10$			
	Treatment:		$F = 27{\cdot}8$, $P = 0{\cdot}0009$			
	Interaction:		$F = 0{\cdot}88$, $P = 0{\cdot}49$			
Cosinor	Lignocaine alone:		$P = 0{\cdot}28$ $\varnothing = 09{\cdot}59 \pm 1{\cdot}57$ $M = 147{\cdot}7 \pm 5{\cdot}6$			
	Lignocaine + flumazenil:		$P = 0{\cdot}79$ $\varnothing = 06{\cdot}22 \pm 5{\cdot}17$ $M = 119{\cdot}2 \pm 3{\cdot}2$			

convulsant activity is significantly increased when flumazenil is injected at 0800, 1000, 1300 and 1800 h; thus, the drug interaction appears to be circadian time-dependent.

Yokoyama et al (1992) recently reported the lack of effect of flumazenil (0·1 mg kg^{-1}) on lignocaine-induced convulsions in rats: our previously reported data (Bruguerolle & Emperaire 1992) on the effect of flumazenil on lignocaine-induced convulsions in mice do not agree with these results: differences in the doses used in the two respective studies may explain such a difference.

The circadian time-dependent drug interaction documented in the present study may be explained by pharmacokinetic changes related to the hour of injection of both drugs; previously reported data on the influence of the hour of injection of local anaesthetic agents on their plasma, heart and brain levels (Prat & Bruguerolle 1990) indicated a significant temporal change of the brain passage of these drugs with higher values observed at 1000 h for bupivacaine and mepivacaine. Other workers (Klotz et al 1985) have found no significant effect of flumazenil on benzodiazepine kinetics. The pharmacokinetic effect involved in the presently reported circadian time-dependent drug interaction still remains to be documented.

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References

Bruguerolle, B., Emperaire, N. (1991) Flumazenil and bupivacaine-induced toxicity: inverse agonist type activity. Life Sci. 49: 185–188

Bruguerolle, B., Emperaire, N. (1992) Local anaesthetics-induced toxicity may be modified by low doses of flumazenil. Life Sci. 50: 185–188

Bruguerolle, B., Prat, M. (1987) Temporal changes in bupivacaine kinetics. J. Pharm. Pharmacol. 39: 148–149

Klotz, U., Duka, T., Dorow, R., Doenicke, A. (1985) Flunitrazepam and lormetazepam do not affect the pharmacokinetics of the benzodiazepine antagonist Ro 15-1788. Br. J. Clin. Pharmacol. 19: 95–98

Lutch, E., Morris, R. (1967) Circadian periodicity in susceptibility to lidocaine hydrochloride. Science 156: 100–102

Prat, M., Bruguerolle, B. (1990) Temporal variations of brain tissue levels of the three local anaesthetics in the mouse. Ann. Rev. Chronopharmacol. 7: 261–264

Yokoyama, M., Benson, K., Arakawa, K., Goto, H. (1992) Effects of flumazenil on intravenous lidocaine-induced convulsions and anticonvulsant property of diazepam in rats. Anesth. Analg. 75: 87–90

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Book Review

Receptor-Ligand Interactions. A Practical Approach
Edited by E. C. Hulme
Published 1992 Oxford University Press, Oxford
XX + 458 pages
ISBN 0 19 963091 7 (pbk) £25.00

My first reaction to opening the package containing the complimentary copy of the book was despair—a couple of weeks earlier I had ordered it on recommendation from a colleague. My second thought was that the book was a lot thicker than I expected! The book is edited by Ed Hulme—a very well respected grinder-and-binder and most of the chapters are written by scientists with comparable standing. The book covers many of the areas associated with ligand binding to homogenate preparations in depth and detail but disappointingly only briefly describes protocols for the performance of quantitative receptor autoradiography. The chapters guide the reader from techniques concerning tissue preparation to more complex issues about mathematical interpretation of the generated data. In addition to the more common uses of the ligand binding technique, the book also describes the use of antibodies and neurotoxins to probe receptor characteristics.

The book starts with an interesting chapter on the methods employed to synthesize radioligands and, whilst the majority of binders are more likely to utilize commercial sources for their radioligands, this is an area of knowledge all too often neglected by graduate students. The subsequent chapters comprehensively cover the important issues concerning the ligand binding technique. Of particular note is the 4th chapter by Ed Hulme and Nigel Birdsall which forms about one-quarter of the book—it provides an extensive review of the strategies, procedures and potential artefacts associated with radioligand binding (essential reading for all novice binders).

I liked the depth of knowledge in most of the chapters in this book. For instance, many previous books skip over the various practical approaches to the different methods applied to separate the bound from free radioligand (filtration, centrifugation, charcoal adsorption, gel-filtration) but this book includes chapters on each individual technique. Whilst this may not be considered essential reading by all, it at least provides an excellent reference for these techniques.

I also liked the chapters concerning the mathematical interpretation of data, which inevitably will only be avidly read by the purist, but the authors usefully provide summary tables which include the principal equations—which are all too commonly misused! The 'mathematical chapters' (which extensively cover interpretation of kinetic data and data obtained at equilibrium), however, like most books on this subject use mainly theoretical examples to illustrate the equations—it would also have been nice to see the use of real data which would allow the reader to perhaps grasp some of the concepts more easily and to place some of the modifications in the binding data, due to various factors, in perspective.

I did not like the inclusion in the book of two extensive appendices written by employees of Amersham International plc and Du Pont-NEN, respectively. These accounted for about one-tenth of the whole book and only regurgitate the information contained in their respective catalogues which are available free of charge and are likely to be more up to date—indeed this is referred to in the preface!

The Practical Approach series of books published by IRL Press are usually good value and this new member to the family is no exception. I strongly recommend purchase of this book, not only as a reference text to the technique of radioligand binding but also for the essential reading it provides to newcomers who wish not only to generate binding data but also want to interpret the results!

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Book Review

Caffeine, Coffee and Health
(Monographs of the Mario Negri Institute for Pharmacological Research, Milan)
Edited by Silvio Garattini
Published 1992 Raven Press, New York
432 pages
ISBN 0 88167 961 5 $124.00

Caffeine, Coffee and Health is a compendium aimed at scientists already engaged in research on coffee/caffeine and neophytes who wish to acquire up-to-date knowledge of this area. The first three chapters are thorough, well-referenced and paint a clear picture of the complex nature of the pattern of coffee consumption, its chemical composition and the fate of coffee constituents in the body. There follows an excellent chapter on the mechanism of action of caffeine, and other xanthines such as theophylline. Caffeine has a multitude of pharmacological effects, many of which can be explained by blockade of adenosine receptors; but other actions on phosphodiesterases and calcium storage cannot be ruled out.

Chapters six to eight deal with the cardiovascular effects of caffeine, and critically review the evidence for involvement of coffee and caffeine in cardiovascular disease. In non-coffee drinkers, caffeine induces pressor effects with biphasic changes in heart rate and increases in plasma catecholamine concentrations and renin activity. Interestingly, tolerance to these effects develops after three to four days of coffee consumption. There is evidence that habitual drinking of large amounts of coffee increases the risk of coronary heart disease and acute myocardial infarction; but heavy coffee consumption is associated with cigarette smoking, which complicates interpretation of epidemiological studies on this subject.

The psychopharmacology of coffee and caffeine is considered in great detail in chapters nine to eleven. The effects of caffeine on behaviour are subtle, and are usually observed only after doses equivalent to several cups of coffee. Caffeine is anxiogenic; it increases sleep latency and can improve performance of a variety of sustained tasks. Though caffeine is often classified as a psychostimulant such effects are, at best, modest and it is suggested that caffeine should be viewed as a "stabilizer of freshness" rather than as a stimulant. By contrast to previous sections, I found this part of the book difficult to assimilate. This was largely due to my ignorance of the subject matter; but in addition, the text was prosaic and data were not presented in an imaginative manner. Chapters nine to eleven destabilized my freshness since I drank more cups of coffee poring over these chapters than I consumed reading the rest of the book.

The final four chapters review the effects of caffeine on reproduction in animals and man, experimental studies on carcinogenicity and mutagenicity of caffeine and finally, epidemiology of coffee and cancer. Coffee has little effect on the fertility of male and female rodents; but although high doses of caffeine are weakly teratogenic in rodents, no relationship has been found in man between caffeine consumption and embryo toxicity. Epidemiological studies have not detected increased risk of common cancers in coffee drinkers and, although the incidence of bladder cancer is higher in heavy drinkers, this might be explained by the smoking habits of this group. These chapters are concise, well organized and provide objective information on each topic.

Coffee, Caffeine and Health is a valuable addition to the literature on coffee and caffeine. The text is clear and the subjects are presented in a logical order. Overall, the book achieves its aims of distilling a diffuse literature into a single up-to-date text which has sufficient detail for the specialist, while providing a primer for any scientist interested in its subject matter.

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