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GABA receptor subunits and global behaviour

The $GABA_A$ receptor complex is one of the most important brain receptors, with nearly one third of brain synapses being GABAergic [1]. Therefore, the powerful inhibition mechanisms that they induce affect many behavioural phenomena, such as sedation, a lowering of anxiety, stopping epileptic seizures, myorelaxation, anaesthesia and impairment of learning processes. Conversely, drugs that reduce GABA inhibition have the opposite, i.e. 'excitatory', effects, ranging from greater anxiety to enhanced learning. The discovery of $GABA_A$ receptor subunits offered the possibility for analytical interpretation of these effects by linking a specific behaviour pattern to a specific receptor subunit – a possibility that has now been realised. The use of genetically modified mice, brilliantly reviewed by Whiting in a recent issue of *Drug Discovery Today* [2], made it possible to study behaviour in the absence of a given subunit. This led to the discovery of the probable involvement of $\alpha 1$ and $\beta 2$ subunits in sedation, of $\alpha 2$ in anxiety and myorelaxation, of $\alpha 5$ in learning, of $\beta 3$ in anaesthesia, of δ in epileptic seizures and so on. Expectations for improving this analytical knowledge are well-founded and have opened the path to further prospects of discovering promising new, more specific, GABA-acting compounds. Specific behaviour patterns might even be explained in terms of combinations of receptor units.

At this stage of research, however, these superb analytical results must not overshadow a broader, all-encompassing assessment of behaviour. It has been shown, for example, that nonspecific GABA agonists (e.g. benzodiazepines) or inverse agonists (e.g. various β-carbolines) can affect anxiety, epileptic seizures and even learning [3]. Although these behavioural traits can be specifically related to $\alpha 2$, δ and $\alpha 5$ subunits, respectively, the link between them might be of physiological importance. It could be physiologically relevant that anxiety is involved in seizuring mechanisms [4] and that mild anxiety could be useful in improving learning processes [5]. Similar considerations are likely to apply to sedation and anxiolysis, or sedation and anaesthesia. The analytical data cited here should therefore be integrated into an overall assessment, because behaviour is both a collection of independent units and a collection of integrated patterns. The functioning of the body is both autonomous within its diverse components and integrated as a whole [6]. The useful discovery of selective ligands of $GABA_A$ receptor subunits does not, therefore, preclude the important role that is played by broadly and biologically active compounds that target several subunits at the same time and induce a number of multimodal behavioural regulations.

References

1 Costa, E. *et al.* (1975) Evidence for involvement of GABA in the action of benzodiazepines: study on rat cerebellum. In: *Mechanism of action of benzodiazepines* (Costa E. and Greengard P. eds), pp 113–130, Raven Press

2 Whiting, P.J. (2003) GABA-A receptor subtypes in the brain: a paradigm for CNS drug discovery? *Drug Discov. Today* 8, 445–450

3 Venault P *et al.* (1986) Benzodiazepine impairs and ß-carboline enhances performance in learning and memory tasks. *Nature* 321, 864–866

4 Chapouthier, G. and Venault, P. (2001) A pharmacological link between epilepsy and anxiety? *Trends Pharmacol. Sci.* 22, 491–493

5 Chapouthier, G. and Venault, P. (2002) GABA-A receptor complex and memory processes. *Curr. Top. Med. Chem.* 2, 841–851

6 Chapouthier, G. (2001) *L'homme, ce singe en mosaïque.* Odile Jacob, Paris

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Strategies for nicotine replacement therapy

Recently recognized as an addictive drug, nicotine remains the habit of choice for hundred of millions of people worldwide. As a result, tobacco-induced death will continue to be a major health problem for decades to come. Until now, the only strategy for overcoming nicotine dependence was substitutive intake, via patches, gums and sprays, intended for use in progressively declining concentrations leading up to definitive withdrawal [Nicotine Replacement Therapy (NRT)]. When

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developing drugs for most pathologies, one of the first parameters to be investigated is the pharmacokinetic profile of the molecule. Rapidly metabolized molecules are not desirable because an active and steady-state plasma concentration would not be reached, even with repetitive intakes. Such molecules are, therefore, discarded or chemically modified to improve their metabolic stability.

In smokers, plasmatic concentrations of nicotine fluctuate around a 100 nM baseline, with a several-hundred-nanomolar peak after initial intake. However, recent work by Edward Sellers and co-workers indicates that individuals vary in their ability to metabolize nicotine, according to cytochrome P450 2A6 (CYP2A6) polymorphism (CYP2A6 is the major nicotine-metabolizing enzyme). Individuals who metabolize nicotine slowly smoke less, are less dependent and have an increased probability of success when they decide to give up [1]. Thus, Sellers *et al.* propose an investigation into the 'beneficial' effect of CYP2A6 inhibitors in NRT. The use of such compounds could artificially elevate the plasmatic nicotine concentrations at equivalent intake doses and, thus, might help to reduce withdrawal symptoms.

The use of an additive compound in NRT has already been successful, with the monoamine uptake inhibitor bupropion. To understand the logic of this approach and to highlight possible alternative strategies, it is worth recalling the basic mechanisms that mediate the major effects of nicotine. Nicotine is an alkaloid that binds specifically to central nicotinic acetylcholine receptors (nAChRs), a subclass of ligand-gated channels that are involved in direct synaptic transmission and synaptic modulation [2]. They contain α4 and β2 subunits; knockout experiments, in which these subunits were deleted, have demonstrated the role of α4β2 nAChRs in mediating the effects of nicotine [3]. There has been strong debate concerning the molecular action of nicotine on α4β2 nAChRs because chronic exposure to nicotine has been shown to up-regulate the function of human α4β2 nAChRs *in vitro* [2]. The α4β2 nAChR is expressed on dopaminergic pre-synaptic boutons (ventral tegmental area, striatum) and can enhance the release of dopamine, which, ultimately, triggers and maintains addiction mechanisms. Bupropion works by enhancing the dopamine concentration at synaptic clefts and, thus, mimicking this nicotinic effect. More recently, Lynx1 (an endogenous prototoxin identified in rodent brain) has demonstrated an opposite effect to that of nicotine on the α4β2 nAChR [4] and might, therefore, constitute another target for NRT approaches.

As discussed by Sellers and co-workers, it should also be noted that 17β-estradiol is a positive allosteric modulator of α4β2 nAChRs [5,6], whereas progesterone is a negative one [7]; hence, natural or synthesized steroids might constitute additional enhancers of NRT. Finally, as highlighted for CYP2A6, we should bear in mind that polymorphisms probably exist for most of the proteins implicated in the nicotine addiction mechanisms.

References

1 Sellers, E.M. (2003) Decreasing smoking behaviour and risk through CYP2A6 inhibition. *Drug Discov. Today* 8, 487–493

2 Buisson, B. and Bertrand, D. (2002) Nicotine addiction: the possible role of functional upregulation. *Trends Pharmacol. Sci.* 23,130–136

3 Marubio, L.M. and Changeux, J.P. (2000) Nicotinic acetylcholine receptor knockout mice as animal models for studying receptor function. *Eur J Pharmacol.* 39, 3113–3121

4 Ibanez-Tallon, I. *et al.* (2002) Novel modulation of neuronal nicotinic acetylcholine receptors by association with the endogenous prototoxin lynx1. *Neuron* 33, 893–903

5 Paradiso, K. *et al.* (2001) The C terminus of the human nicotinic alpha4beta2 receptor forms a binding site required for potentiation by an estrogenic steroid. *J. Neurosci.* 21, 6561–6568

6 Curtis, L. *et al.* (2002) Potentiation of human alpha4beta2 neuronal nicotinic acetylcholine receptor by estradiol. *Mol. Pharmacol.* 61, 127–135

7 Valera, S. *et al.* (1992) Progesterone modulates a neuronal nicotinic acetylcholine receptor. *Proc. Natl. Acad. Sci. U S A* 89, 9949–9953

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