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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 $\delta$ 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 $\alpha 2$, $\delta$ 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.

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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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