The conductance of extrasynaptic $GABA_A$ channels in newborn rat hippocampal neurons is increased by alphaxalone and pregnanolone

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$GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the brain. They form chloride ion channels that are opened by GABA and modulated by a variety of clinically important drugs such as anaesthetics, convulsants and barbiturates. $GABA_A$ receptors are found both at the synapse and non-synaptically on the cell body. It has been suggested that non-synaptic $GABA_A$ receptors may provide a tonic background inhibition of neurons. It is these receptors that are normally studied using isolated patch techniques. Neuroactive steroids are a group of potent modulators of $GABA_A$ receptors. In this study single channel chloride currents activated by GABA were recorded in cell-attached and inside-out patches from cultured hippocampal neurons obtained from newborn rats after they were decapitated using protocols approved by the Animal Ethics Committee (JBM) of the Australian National University and Heidelberg University. The effects of the anaesthetic neurosteroid alphaxalone and the endogenous steroid pregnanolone were tested on $GABA_A$ channels. Alphaxalone at concentrations above 1 μM, and pregnanolone at 0.1 μM, increased the conductance of channels activated by GABA. Both steroids at higher concentrations could directly activate chloride channels and generally these channels exhibited a high conductance. The directly activated channels were modulated by diazepam and it was concluded that they were $GABA_A$ channels. An important site of action of neurosteroids may be extrasynaptic $GABA_A$ receptors.