Chapter 9
Pregnane Steroids and Short-Term Neural Plasticity

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Abstract  Gamma-aminobutyric acid (GABA) is the major inhibitory transmitter in the brain, and its fast effects are mediated by the GABA-A receptor. It is well known, from pharmacological manipulations, that many exogenous agents alter the efficacy of GABA-A receptors. For example, benzodiazepines increase the effect of GABA and some \( \beta \)-carbolines reduce the effect of GABA at these receptors. Increasing the strength of neuronal inhibition can prevent seizures, reduce anxiety and be neuroprotective. There are also endogenous mechanisms that increase efficacy. For example, more GABA-A receptors can be synthesized and inserted into synapses, but this requires up to 1 h or more. On a shorter timescale, GABAergic inhibition can be potentiated by steroids, e.g., allopregnanolone, synthesized \textit{de novo} in neural tissue or derived from peripheral endocrine organs. The widespread distribution of these neuroactive steroids across the brain suggests an extensive role in short-term neural plasticity.

Keywords  Allopregnanolone, allotetrahydrodeoxycorticosterone, GABA, gain control, homeostasis

Abbreviations  Allopregnanolone 3\( \alpha \)-hydroxy-5\( \alpha \)-pregnan-20-one; alloTHDOC 3\( \alpha \),21-dihydroxy-5\( \alpha \)-pregnan-20-one; CNS central nervous system; DBI diazepam binding inhibitor; 5\( \alpha \)-DHDOC 5\( \alpha \)-dihydrodeoxycorticosterone; 5\( \alpha \)-DHP 5\( \alpha \)-dihydroprogesterone; DNLL dorsal nucleus of the lateral lemniscus; GABA \( \gamma \)-aminobutyric acid; 3\( \alpha \)HSD 3\( \alpha \)-hydroxysteroid dehydrogenase; 5-HT 5-hydroxytryptamine; ICC inferior colliculus; IPSC inhibitory post-synaptic current; KA kainic acid; MBR mitochondrial benzodiazepine receptor; P450scc cytochrome P450 side chain cleavage enzyme; SNR substantia nigra pars reticulata; StAR steroid acute regulatory protein; Wm white matter

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9.1 Introduction

Changes in the efficacy of synaptic transmission between neurons is thought to underlie learning and memory formation,1,2 a number of disease states and the counteractions for homeostasis,3 and aging processes.4 These changes, also known as plasticity, take various forms, occurring over different timescales. Known mechanisms include changes in the amount of transmitter released (which can increase in less than 1 s and last minutes5), to the synthesis of proteins such as receptors, taking tens of minutes or more and having long-term effects.6 In this chapter, we will focus on a mechanism for the plasticity of inhibitory inputs, lasting minutes to tens of minutes. Critical during this period are the endogenous pregnane steroids 3α-hydroxy-5α-pregn-20-one (also known as 3α,5α-tetrahydroprogesterone or allopregnanolone; Fig. 9.1) and 3α,21-dihydroxy-5α-pregn-20-one (also known as 3α,5α-TetraHydroDeOxyCorticosterone or alloTHDOC). These are potent modulators of inhibitory neurotransmission.

9.2 Pregnane Steroid Synthesis and Metabolism

Pregnane steroids are derived from cholesterol (Fig. 9.2). The putative rate-limiting step in their synthesis is the conversion of cholesterol to pregnenolone by the cytochrome P450 side chain cleavage enzyme7 (P450scc). This is dependent upon the steroid acute regulatory protein (StAR), in co-operation with the diazepam binding inhibitor (DBI) and the mitochondrial benzodiazepine receptor (MBR), facilitating cholesterol transport to P450scc in the inner mitochondrial membrane.8,9 The aforementioned neurosteroid synthetic machinery, and the enzymes downstream in the

![Fig. 9.1 Chemical structure of allopregnanolone. The four carbon rings of the steroid are labelled A–D, with carbon atoms numbered as shown. Dashed lines denote a chemical group below the plane of the ring system, i.e., the α configuration. The compound illustrated is 3α-hydroxy-5α-pregn-20-one, also known as allopregnanolone](image-url)