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The neurobiology of the male sexual refractory period

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ABSTRACT

Despite having been recognized for many years, the mechanisms governing the male sexual refractory period (post-ejaculatory refractory period, post-ejaculatory interval) remain poorly understood. This review examines the brain and spinal areas putatively involved in this phenomenon to draw a coherent picture from the available data. It is hoped that this will reveal where further research will offer the potential for crucial insights on this topic.

1. Introduction

If we consider, in various species, all of the males in the world that have a penis, it would seem that it is incumbent upon them to achieve an erection and ejaculate in order to impregnate a female. The former requirement is relaxed in the case of males that do not have a penis. From an evolutionary perspective, these mechanisms should be robust. In humans perhaps these are robust enough, but there are nonetheless examples where one or the other does not work. Moreover, both are susceptible to pharmacological intervention: numerous medications and recreational drugs can inhibit erection (McVary, 2007) and/or ejaculation (Jenkins and Mulhall, 2015).

If we consider the period of sexual quiescence following ejaculation – the sexual refractory period (SRP) – it is not immediately clear why this should be required to impregnate a female. This feature of the male sexual response cycle is highly conserved among species (see Section 2.5) and highly robust. Compared to erectile dysfunction and anorgasmia, the lack of an SRP is quite uncommon (Wibowo and Wassersug, 2016). The SRP also is remarkably resistant to pharmacological intervention (see Section 4). An understanding of the mechanism of this has been elusive, so the variety of actors involved in this process is the subject at hand; this review seeks to enumerate and link the data connecting them.

2. The nature of the refractory period

Before discussing its traditional place within the sexual response cycle of men, I would like to propose that the phenomenon be referred to as the sexual refractory period or SRP. Previous work has referred to this as the male refractory period or post-ejaculatory refractory period, and the use of these terms implicitly characterizes the SRP as unique to men. First, it is not clear that this implication is rigorously true, though sexual dimorphism certainly exists (Section 2.4). Second, this may subtly discourage research into the SRP and other post-orgasm phenomena in women. Though I advocate this gender-neutral terminology, there is vastly more literature on this subject pertaining to males, so a majority of the discussion will focus on males, whose SRP is considerably more pronounced. Moreover, where direct comparison is possible, the data point to a mechanism that operates in males but not in females. I would like to note that the term 'post ejaculatory interval' or PEI refers to a phase in the sexual response of male animals (oftentimes rats in the context of this subject), whose name is unquestionably an apt descriptor of the phenomenon, see Section 2.5). Here we will use the term sexual refractory period in conjunction with humans and post ejaculatory interval in conjunction with animals.

2.1. Place in the sexual response cycle

Orgasm and/or ejaculation is followed by the induction of several phenomena that serve to suppress the ability to perform sexually. These common features comprise the sexual refractory period in men, and are (1) inhibition of erection, (2) inhibition of orgasm or ejaculation, and (3) decrease in arousal/suppression of arousability. Along with the commonly reported aspects of the SRP are ones that appear to be somewhat less general features of the post-orgasm state. Among these are genital hypersensitivity and sometimes depression, experienced in both men and women, though not universally. Clearly, these less general features can also serve to limit further sexual response, albeit indirectly. However, their lack of both generality and a direct inhibitory mechanism on sexual response suggest that they may be better

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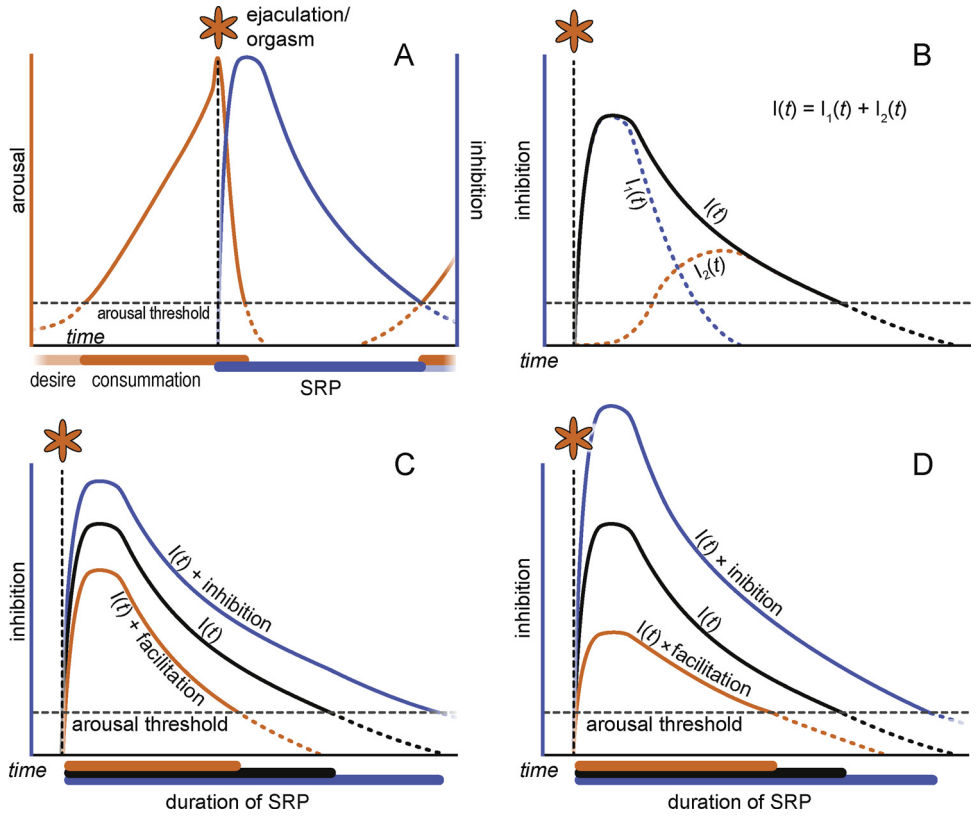

Fig. 1. A: The SRP's relationship to the sexual response cycle. B: The inhibition curve as a sum of components. C: How interventions can change the duration of the SRP without changing its mechanism. D: How interventions that directly affect the mechanism of the SRP can change its duration.

characterized as responses to orgasm rather than defining components of the SRP per se. Nonetheless, it can be put most succinctly that the SRP serves to halt forward progression in the sexual response cycle.

2.2. Graphical representation of the SRP

Actually, that is not quite true. The SRP is only an interval of time, so it is the processes and their attendant inhibition that are responsible for the observed effects rather than the time itself. Therefore, I believe that understanding of the SRP has been prejudiced and compromised by the notion that it can be described by a one-dimensional bracketed region of the sexual response cycle (arousal vs. time) in the dimension of time (Levin, 2009) or arousal (Masters and Johnson, 1966). These will not suffice.

To understand the biology of the SRP, we are better served by conceptualizing it in two dimensions as inhibition as a function of time, y = I(t) (Fig. 1). While the unitless axis of inhibition is necessarily vague, this model nonetheless serves some important purposes. This is likely a better descriptor of the neural activity that results in the inhibition that characterizes the SRP; after all, the SRP is a matter of degrees and not absolutes – a notion that is borne out by behavioral observations (Dunn and Trost, 1989; Masters and Johnson, 1966).

The two-dimensional model does not suggest that something that changes the length of the SRP necessarily augments or attenuates its attendant inhibition: faciliatory interventions may make it easier to overcome the inhibition of the SRP as it declines with time, and the converse can be true of inhibitory interventions (Fig. 1A). Also, it is possible to think of the SRP as a sum of inhibitory components (i.e. $I(t) = I_1(t) + I_2(t) + I_3(t) + \ldots$) rather than the product of a single process. Importantly, these components need not be scalar multiples of each other; they may each have different relative contributions at different times, perhaps reflecting the contributions of synaptic transmission versus an endocrine mechanism.

In fact, such a separation of terms may be appropriate even for a single neurotransmitter within a small region of the brain. Hull and coworkers have proposed (Dominguez and Hull, 2005) that some of dopamine's pro-sexual effects in the medial preoptic area (mPOA) are due to it attenuating the effect of GABAergic tonic inhibition in this area (see Section 4.3). A drop in mPOA dopamine concentrations could therefore indicate a return of tonic inhibition, and this would be slower than an effect due to direct synaptic transmission. Such an effect could come about by phasic, GABAergic inhibition (see Section 4.7), a mechanism suggested by the work of Fernandez-Guasti (Fernández-Guasti et al., 1986).

The similarity between panels C and D of Fig. 1 illustrate the difficulty of positing a role for a certain pathway or neurotransmitter based on behavioral observations alone: the length of the refractory period in each case remains the same. Nonetheless, the mechanistic implications of each differ significantly. In the case where an intervention does not interact with the operative pathway of the SRP, the effects would be expected to sum. This may be at work with the dopaminergic agents L-DOPA, a dopamine precursor, and apomorphine, a relatively non-specific DA agonist (Paglietti et al., 1978). Each of these substantially shortens the PEI of rats, but each also increases other measures of sexual function. Thus, each one acts as a faciliatory agent in the absence of SRP-related inhibition meaning that neither can act solely to block the latter. At the extreme represented in panel C, this facilitation occurs at a constant level regardless of the SRP resulting in a sum of the two effects. This does not preclude DA from being involved in the mediation of downstream effects in the SRP, but it is an indication to look elsewhere for the ultimate cause of these effects.

This contrasts to the scenario depicted in panel D. If an agent manifests its effects only in the presence of SRP-related inhibition, then the two would be unlikely to act independently. In a simplified case, a faciliatory agent should halve the height of the inhibition curve at all points. Again, it is necessary to draw contextual clues to determine if